"Segmental Neuralgia in Painful Syndromes"

This work is based upon the fact that, clinically the combination of segmental pain and tenderness usually is due to factors which irritate roots, ganglia or trunks of the spinal sensory nerves, and not due to painful impulses originating in diseased viscera. The authors emphasize that the various forms of therapy should be applied to the source of pain and not to areas of referred pain where treatment is of little value. Just how to examine the patient, the methods of eliciting tenderness, the various forms of therapy employed and how and where to apply them are so clearly described and illustrated that every physician can readily adapt them to his own methods."

320 Pages 178 Illustrations $5.00

— By —

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DIABETES MELLITUS WITH CARCINOMATOSIS AND MANY OTHER UNEXPLAINED COMPLICATIONS: A CASE REPORT WITH AUTOPSY FINDINGS

WILLIAM BALDWIN, JR.
Professor of Physiology

Mrs. S., an obese female aged sixty-three, was first seen in January 1941. Her chief complaint was generalized pruritus, polyuria and polydipsia. This condition had been present for several months. She reported that the itching was very annoying, not localized to any one part of the body, and not constant. There were no skin changes or markings at the sites of itching. There was polydipsia and polyuria, with a urinary frequency of 2 or 3 times a night, and 8 to 10 times a day. There was no pain or burning on urination, and no difficulty in starting or stopping the flow of urine. There was no history of hematuria.

Family History

Father died at age 37 of tuberculosis of the larynx. Mother died at age 85 of carcinoma of the right breast, and heart disease. Two brothers living, one diabetic, the other possibly tuberculous. One sister living, hypothyroid, and with past history of Bright’s disease. No history of allergy or gout.

Past History

Patient had measles, chicken pox, mumps, whooping cough at age 35, “stomach trouble” at 32, and diabetes mellitus at age 19 “cured by an herb imported from France.” No history of rheumatic fever or scarlet fever. She does not use tobacco or alcohol, and drinks 2 or 3 cups of coffee daily.

She has been constipated for years necessitating the use of laxatives. She has intolerance for fatty foods, has occasional pain under the right costal margin anteriorly, has considerable flatulence, and an occasional clay colored stool, but there is no history of bloody or tarry stools. She has been told in the past that she had cirrhosis of the liver. Though obese, she has been unable to lose weight by restricting her diet.

She has occasional colds, and suffers from hay fever which is very severe, lasting from August 15, to October 15 every year.

Menopause occurred at age 52 and was asymptomatic. She has never been pregnant.

Physical Examination

An obese woman of 63, weighing 210 pounds. The ears, eyes, nose and throat were negative except for injection of the nasal mucous mem-
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She has occasional colds, and suffers from hay fever which is very severe, lasting from August 15, to October 15 every year.

Menopause occurred at age 52 and was asymptomatic. She has never been pregnant.

Physical Examination

An obese woman of 63, weighing 210 pounds. The ears, eyes, nose and throat were negative except for injection of the nasal mucous mem-
brane. No masses were noted in the breasts. The heart was within normal percussion limits. The aortic sounds were roughened, and there was a presystolic mitral murmur.

The systolic blood pressure was 135 and the diastolic 95 in the right arm. In the left arm the corresponding pressures were 132 and 93. The pulse was 68, and the temperature 97.6° F. The lungs were negative. The abdominal muscle tonus was poor, the J. B. Murphy's sign positive, but Lloyd's and McBurney's signs were negative. The pelvis showed senile changes, but was otherwise essentially negative.

**Laboratory Findings:**

The 24 hour specimen of urine had a volume of 2100 cc., a specific gravity of 1.006, and was positive to 1 drop by Benedict's method. A fasting blood sugar was 320 mg. per 100 cc., and the basal metabolic rate was minus 8 per cent.

**Treatment and Progress:**

A diagnosis of diabetes mellitus, allergy, and chronic cholecystitis was made. X-ray examination of the gallbladder was advised, but the patient refused to have this work done. The diabetes was brought under control by diet plus 20 units of protamine zinc insulin once daily. The urine continued, however, to remain positive to 1 drop even though the blood sugar level was reduced to 135.

The patient was treated with manipulative therapy once weekly, and with Preitz displacement treatment during the hay fever season. Clinically, she seemed improved, and reported that she felt much better.

In June 1941 she complained of some abdominal distress and reported that one morning, in spite of the fact that she had taken a laxative the night before, she had no passage of stool, and had considerable abdominal pain and distension. The patient administered an enema to herself, after which a hard mass was expelled. Following the passage of a small hen's egg. Following the passage of the stone the abdominal distress disappeared, and the patient again reported that she felt well. X-ray study made with contrast media showed a nonvisualizable gallbladder and a cholecystoduodenal fistula.

Under dietary control the weight was gradually reduced during the next year to 180 lbs. On June 19, 1942, the patient was seen, complaining of abdominal pain, nausea, vomiting and obstipation. The abdomen was markedly distended, rigid, and very tympanitic. The patient failed to respond to conservative measures, and when the vomitus showed fecal characteristics, she was admitted to the hospital on June 21, 1942 with a diagnosis of intestinal obstruction.

**TABLE 1**

<table>
<thead>
<tr>
<th>Date</th>
<th>Hemoglobin %</th>
<th>Color Index</th>
<th>Erythrocytes in millions</th>
<th>Leucocytes</th>
<th>Lymphocytes</th>
<th>Mononuclears</th>
<th>Neutrophiles</th>
<th>Multiple Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>1942</td>
<td>109.50</td>
<td>1.0</td>
<td>6.26</td>
<td>6.00</td>
<td>2.700</td>
<td>130</td>
<td>3120</td>
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<td>83.95</td>
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<td>8.600</td>
<td>2.306</td>
<td>86</td>
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<tr>
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<td>87.60</td>
<td>1.0</td>
<td>4.23</td>
<td>6.300</td>
<td>2.646</td>
<td>0</td>
<td>3654</td>
<td>2.5</td>
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<td>11</td>
<td>7.30</td>
<td>0.8</td>
<td>4.34</td>
<td>10.000</td>
<td>4.000</td>
<td>100</td>
<td>5800</td>
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<tr>
<td>Nov. 11</td>
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<td>0.9</td>
<td>4.30</td>
<td>12.500</td>
<td>1.750</td>
<td>500</td>
<td>10000</td>
<td>0.9</td>
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<tr>
<td>Jan. 11</td>
<td>91.25</td>
<td>0.9</td>
<td>5.06</td>
<td>13.500</td>
<td>2.700</td>
<td>135</td>
<td>10665</td>
<td>2.6</td>
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<tr>
<td>Mar. 21</td>
<td>68.7</td>
<td>0.9</td>
<td>3.60</td>
<td>20.000</td>
<td>1.600</td>
<td>400</td>
<td>18000</td>
<td>3.2</td>
</tr>
<tr>
<td>15</td>
<td>69.4</td>
<td>0.8</td>
<td>4.01</td>
<td>8.700</td>
<td>2.088</td>
<td>87</td>
<td>6585</td>
<td>2.0</td>
</tr>
<tr>
<td>22</td>
<td>80.3</td>
<td>0.8</td>
<td>4.06</td>
<td>11.000</td>
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<td>7590</td>
<td>2.0</td>
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<tr>
<td>28</td>
<td>87.6</td>
<td>0.9</td>
<td>4.52</td>
<td>14.500</td>
<td>1.595</td>
<td>0</td>
<td>12950</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Urinalyses on June 21, 26, 29, and July 2, were essentially negative. Blood count was shown in table 1, blood sedimentation was as shown in figure 1. Because of the inability of the patient to retain food, insulin had been discontinued, and on admission the blood sugar level was 268 mg. per 100 cc. During her stay in the hospital the mean temperature was 98° F., fluctuating between 97° and 98.6°. At no time did the diurnal variation exceed 1° F. Pulse varied between 70 and 80 beats per minute. Blood amyrase was 110 mg. per 100 cc.

Treatment consisted of soft tissue manipulation in the splanchnic area three times daily, the use of an oral Wangensteen apparatus, and a rectal tube. One cc. of 1 to 2000 prostigmine was given by hypodermic every 6 hours, and hot turpentine sups were applied to the abdomen for 30 minutes 3 times a day.

The patient improved rapidly, and insulin therapy was reinstated. Following this the blood sugar level fell from 203 mg. per 100 cc. on June 26, to 191 mg. on June 29, and to 152 mg. per 100 cc. on July 1. X-ray examination, as reported below, was carried out by the Department of Radiology and the patient was discharged from the hospital on July 3, 1942.

X-ray examination of the gastro-intestinal tract was made as requested, the examination being initiated June 29th, and completed July 3rd. Re-examination of the small intestine was made following
The systolic blood pressure was 135 and the diastolic 95 in the right arm. In the left arm the corresponding pressures were 132 and 93. The pulse was 68, and the temperature 97.6° F. The lungs were negative. The abdominal muscle tonus was poor, the J. B. Murphy's sign positive, but Lloyd's and McBurney's signs were negative. The pelvis showed senile changes, but was otherwise essentially negative.

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<td>3,120</td>
<td>3.8</td>
</tr>
<tr>
<td>June 21</td>
<td>83.95</td>
<td>0.8</td>
<td>5.00</td>
<td>8,600</td>
<td>2,236</td>
<td>86</td>
<td>6,192</td>
<td>2.0</td>
</tr>
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<td>2,646</td>
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<td>2.5</td>
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<tr>
<td>Sept. 11</td>
<td>73.00</td>
<td>0.8</td>
<td>4.34</td>
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Fig. 1. Erythrocytic Sedimentation Rate.

patient's discharge from the Hospital. This examination being carried out on August 4th and 7th respectively.

Esophagus:—Negative to the passage of liquid barium.

Stomach:—The stomach occupied a high position, conforming to the habitus of the patient. Investigation of the gastric mucosa at screening revealed no changes indicative or suspicious of corpus ulcer or cancer. The filled stomach showed a fairly regular relief and peristalsis was not interrupted. Barium passed through the pylorus to fill a deformed modified post pyloric cap. Palpatory examination was negative for tumor mass and localized pressure tenderness. The duodenum proper showed no fluoroscopic evidence of pathology. Serial films made following fluoroscopic examination showed no filling defects or ulcer niche in the gastric corpus. The post pyloric cap displayed irregular contour and relief and there was demonstrated the presence of a collection of barium, extra-duodenal in location, and assuming a position within anatomic range of the gallbladder. The shape of the extra-duodenal collection did not conform to that of a diverticulum and the appearance of the barium suggested an admixture of either intestinal contents or some other material of other than opaque character. The duodenum appeared to be negative. The mesenteric intestine was fairly motile. In some of the films secured there was questionable variation in mucosal relief and some increase in luminal caliber located to the third group of mesenteric coils in midabdominal location. Some slight tenderness to deep pressure was elicited over the area. These latter findings were best demonstrated at the five-hour period.

At the five-hour examination the stomach was entirely evacuated. In the region of the gallbladder there was a small collection of barium and from the opacity a fine linear collection of barium was seen to extend mesially toward the duodenum. The bulk of the contrast meal was in the terminal ileum. Considerable fecal matter was demonstrated in the cecum and proximal colon at this time. The stomach was refilled and subsequent films and screen investigation confirmed findings noted at morning examination referable to the duodenal and periduodenal areas. There was also again noted modification as to filling and the size of luminal caliber of the third group of mesenteric coils as localized previously. In none of the films was there frank evidence of intestinal obstruction.

Colon:—At the twenty-four hour period contrast barium was demonstrated in the cecum and colon as far distal as the left iliac segment. No barium was demonstrated in the sigmoid or rectum at this time. The colon generally appeared to be fairly mobile. No tumor masses or tender points were elicited. The appendix was not visualized. At forty-eight hours there was a residuum of barium in the cecum and contrast medium was scattered throughout the colon and rectum. All other findings conform to those observed at the twenty-four hour period.

Following catharsis, the colon was further investigated by means of barium enema. Under the fluoroscopic control the contrast fluid filled the rectum and sigmoid readily, with canalization of the colon and cecum accomplished without pathologic delay. The colon showed tendency toward redundancy but presented fairly smooth and regular filling. Films secured immediately after clyisma showed barium throughout the colon, and there was also contrast medium in the terminal ileum. There appeared to be altered filling localized to the ascending colon in its proximal half. This filling defect might be accounted for on the basis of gas or fecal matter. One cannot, however, entirely eliminate the possibility of a mural lesion. The terminal ileum showed altered filling, which might be due to gas since subsequent films failed to confirm the possibility of intrinsic ileal lesion. Following evacuation of the colon, films were secured in three posi-
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tions, which showed elimination of practically all barium from the cecum and colon with the exception of a small amount of contrast medium in the left iliac and pelvic-sigmoid portions of the colon. There was retention of a small amount of barium in the ileum. The appendix was visualized and showed a broken, irregular filling.

**Opinion:**—(1) The stomach insofar as the corpus is concerned, appears negative for cancer and ulcer. There is modification of the post pyloric cap, which assumed a high position to the right, and there is also demonstrated an extraduodenal collection of barium which is visualized as a residuum up to and including the five hour period. I believe consideration should be given here to the possibility of a choledocho-duodenal fistula, and probably adhesions and bands about the cap and duodenum account for the findings previously noted insofar as the anatomic location of these parts is concerned. (2) The possibility of intrinsic colic lesion is suggested but not confirmed on the basis of clysma study. Findings referred to are noted in the ascending portion of the colon. The colon is of a redundant form and is otherwise negative. (3) Broken, irregular residuum of barium located to the appendix prior to and following clysma.

Re-examination of the small intestine was carried out, employing motor meal. One hour following administration of contrast meal the bulk of the medium was demonstrated in the stomach. The head of the progress meal had reached the third group of mesenteric coils. At screening, intestinal motility, while active, appeared to be diminished, considering average. Barium was demonstrated in the appendix, apparently held as a residuum from the motor meal given the patient on August 4th, that is, three days prior to this examination. A three hour study showed approximately 50 per cent of the motor meal in the stomach. Barium was demonstrated in the mesenteric intestine, again as far as the third group of mesenteric coils at mid-abdominal level. At the five hour period approximately 15 to 20 per cent of the meal was retained in the stomach, with contrast medium again demonstrated in the mesenteric intestine, the head of the meal being in the fourth to fifth group of coils, that is, in the ileum proper. At seven hours the stomach showed complete evacuation with a spot residuum of barium located to the region of the duodenal or peri-duodenal area. The bulk of the contrast meal was demonstrated in the third, fourth, fifth and sixth groups of mesenteric coils. Screen examination at this time showed intestinal motility, the flow somewhat rhythmical in the ileum and proportionately so in the region of the third group of coils. There was no evidence of puddling, reverse peristalsis or gross dilatation of the intestine. A twelve hour film showed the head of the progress meal in the descending colon with faint traces of barium in the terminal ileum. The cecum and transverse colic segments contained barium. Palpatory examination during the aforementioned period reveals no essential facts, at least of informative value.

**Opinion:**—Re-examination of the mesenteric intestine fails to confirm evidence of neoplasm or gross evidence of intestinal obstruction. It may be stated, however, that intestinal motility generally is below average, and motor delay is apparent in the ileum up to and including the twelve hour period. The third group of mesenteric coils at mid abdominal level shows delayed motor activity. I am unable to account for this finding definitely at the time of this examination.

After discharge from the hospital convalescence was uneventful and radiographic recheck was performed on August 4 and 7, 1942 as reported above. The diabetic condition was kept under control with 20 units of protamine zinc insulin once daily, although, on periodic check of blood sugar, the urine continued to remain positive to one drop even when blood sugar levels were as low as 130 mg. per 100 cc. The patient had frequent clay colored stools, and considerable flatulence, with minimal abdominal discomfort.
tions, which showed elimination of practically all barium from the cecum and colon with the exception of a small amount of contrast medium in the left iliac and pelvic-sigmoid portions of the colon. There was retention of a small amount of barium in the ileum. The appendix was visualized and showed a broken, irregular filling.

**Opinion**—(1) The stomach insofar as the corpus is concerned, appears negative for cancer and ulcer. There is modification of the post pyloric cap, which assumed a high position to the right, and there is also demonstrated an extraduodenal collection of barium which is visualized as a residuum up to and including the five hour period. I believe consideration should be given here to the possibility of a cholecystoduodenal fistula, and probably adhesions and bands about the cap and duodenum account for the findings previously noted insofar as the anatomic location of these parts is concerned. (2) The possibility of intrinsic colic lesion is suggested but not confirmed on the basis of clysma study. Findings referred to are noted in the ascending portion of the colon. The colon is of a redundant form and is otherwise negative. (3) Broken, irregular residuum of barium located to the appendix prior to and following clysma.

Re-examination of the small intestine was carried out, employing motor meal. One hour following administration of contrast meal the bulk of the medium was demonstrated in the stomach. The head of the progress meal had reached the third group of mesenteric coils. At screening, intestinal motility, while active, appeared to be diminished, considering average. Barium was demonstrated in the appendix, apparently held as a residuum from the motor meal given the patient on August 4th, that is, three days prior to this examination. A three hour study showed approximately 50 per cent of the motor meal in the stomach. Barium was demonstrated in the mesenteric intestine, again as far as the third group of mesenteric coils at mid-abdominal level. At the five hour period approximately 15 to 20 per cent of the meal was retained in the stomach, with contrast medium again demonstrated in the mesenteric intestine, the head of the meal being in the fourth to fifth group of coils, that is, in the ileum proper. At seven hours the stomach showed complete evacuation with a spot residuum of barium located to the region of the duodenal or peri-duodenal area. The bulk of the contrast meal was demonstrated in the third, fourth, fifth and sixth groups of mesenteric coils. Screen examination at this time showed intestinal motility, the flow somewhat rhythmical in the ileum and proportionately so in the region of the third group of coils. There was no evidence of puddling, reverse peristalsis or gross dilatation of the intestine. A twelve hour film showed the head of the progress meal in the descending colon with faint traces of barium in the terminal ileum. The cecum and transverse colic segments contained barium. Palpatory examination during the aforementioned period reveals no essential facts, at least of informative value.

**Opinion**—Re-examination of the mesenteric intestine fails to confirm evidence of neoplasm or gross evidence of intestinal obstruction. It may be stated, however, that intestinal motility generally is below average, and motor delay is apparent in the ileum up to and including the twelve hour period. The third group of mesenteric coils at mid-abdominal level shows delayed motor activity. I am unable to account for this finding definitely at the time of this examination.

After discharge from the hospital convalescence was uneventful and radiographic recheck was performed on August 4 and 7, 1942 as reported above. The diabetic condition was kept under control with 20 units of protamine zinc insulin once daily, although, on periodic check of blood sugar, the urine continued to remain positive to one drop even when blood sugar levels were as low as 130 mg. per 100 cc. The patient had frequent clay colored stools, and considerable flatulence, with minimal abdominal discomfort.
On March 2, 1943 the patient complained of pain in the right flank which was rather constant but did not radiate. Lloyd’s sign on the right side was positive. Intravenous urography was advised and performed by the Department of Radiology on March 17, with the results reported below.

A preliminary survey film of the urinary tract showed the kidneys faintly visualized with no gross evidence of urinary tract calculus present. In the main the kidneys showed a fairly comparable degree of size, and renal position was in keeping with average considering the patient’s habitus.

Serial contrast films showed satisfactory concentration of opaque medium in the left kidney with visualization of the left ureter at the five minute period. There was faint concentration of dye in the right kidney. At ten minutes the right kidney showed further concentration with enlarged, dilated calyces present. The right renal pelvis was not seen at this time. The left kidney showed good visualization. At twenty minutes the right renal pelvis and its calyces were visualized, and the proximal right ureter was seen as far as the fourth lumbar vertebra. The renal pelvis shows evidence of pyelectasis as compared to the contralateral kidney. The infundibulae of the calyces are appreciably widened and dilated and the terminal calyceal relief is lost insofar as normal sharpness and cupping are concerned. The terminal calyces are smoothly rounded and there is no extension of contrast medium visible beyond the limits of the terminal fornical margin of the calyces.

Two erect films were made, the first approximately one minute after the patient assumed an erect position. In this film the left kidney showed complete clearance with excellent transportation of urine from kidney to bladder. The right kidney showed marked retention of contrast urine with faulty emptying of the renal pelvis and calyces demonstrated. The proximal ureter swings well toward midline overshadowing the lateral limits of the fourth and fifth lumbar vertebrae. The distal ureter was partially visualized and showed some increase in luminal caliber, though marked ureterectomy was not in evidence. A second erect film made at the end of four minutes of erect position showed average normal function of left kidney. The right kidney showed a persistent delay in emptying with retention of practically all of the contrast urine, as compared to the twenty and twenty-five minute films. Again the distal right ureter was demonstrated in its lower one-third, and no frank ureterectomy was suggested. In both erect films the lower pole of the right kidney extends approximately 5.5 cm. below the level of the iliac crest, there being evidence of some increased mobility to the right kidney. In addition, there is suggested some slight but perceptible horizontal rotation of the right kidney, which in itself might influence drainage and function. The kidney also tends to overshadow the right psoas muscle, which is preserved and demonstrated.

The urinary bladder does not appear to be enlarged and as visualized showed no frank defect. Following micturition no unusual amount of residual urine was present in the bladder.

**CONCLUSION:** (1) At this time urographic study fails to demonstrate urinary tract calculus. (2) The right kidney shows pyelectasis, impaired function and faulty drainage. There is also suggested some tendency toward increased mobility of the right kidney with tendency toward horizontal rotation, which might be an added factor in the matter of faulty drainage and function.

From a radiological point of view two considerations present themselves concerning the right kidney: first, uropathic changes resulting from peri-ureteric involvement affecting the drainage of the kidney and constituting obstructive mechanism, second, intrinsic inflammatory changes in the kidney, resulting in pyelectasis and disturbance of the calyceal and intrinsic renal anatomy.

In view of the history prevailing in this case of a potential cholecystoduodenal fistula, together with the passage of a large biliary calculus, one may attach significance to the findings noted in the right urinary tract, keeping in mind the upper right quadrant situation, which has been previously demonstrated, both radiologically and on the basis of the patient’s past history.

In view of the above findings urological consultation was obtained and cystoscopy and retrograde pyelography were performed on April 2, 1943, the findings of which are reported below.

In the first film made, opaque catheters are seen in both ureters, the tips of the catheters extending well into the renal regions, and on the right side, the catheter tip bends sharply, projecting itself, as subsequently noted, to the caudal limits of the inferior calyx. No calculus was demonstrated.

Contrast films of the right kidney show undoubted evidence of pyelectasis, the enlargement being generalized to the renal pelvis and infundibula with the papillary or fornical portions of the calyces showing a rounded bulbous relief. There was no extension of contrast medium beyond the papillary limits of the calyces. Following withdrawal of the opaque catheters, a film was secured which showed the proximal half of the right ureter demonstrated. There was no opaque medium in the distal right ureter or bladder.

**CONCLUSION:** Right pyelectasis, with no evidence of calculus or tumor or destructive inflammatory pathology present in the right kidney at this time.

Urine obtained by catheter from the right kidney showed a 2 plus reaction to albumin with an occasional pus cell and cast. On the basis of the cystoscopic and radiographic findings, diagnosis of right pyelectasis and pyelonephritis was made. It was felt that this represented a medical rather than a surgical problem, and the patient was treated with nitrohydrochloric acid. Clinical response was excellent.
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The patient remained about the same clinically until December 16, 1943, when she again complained of obstipation and generalized pain in the abdomen. The abdomen was hard and distended, and both dullness and tympany were elicited on percussion. The patient received manipulative therapy twice daily and 1 cc. of 1 to 2000 prostigmine bromide supplemented by oral dosage of prostigmine bromide. The patient, at this time, reported a history of nocturnal dyspnea of four weeks duration. She was hospitalized on December 20, 1943. Since she was unable to take food by mouth the insulin was temporarily discontinued. Survey films of the abdomen were made which suggested the presence of ascites, but did not indicate the presence of intestinal obstruction.

Treatment instituted consisted of the use of an oral Wangensteen apparatus, a rectal tube, and hot turpentine stupes applied for 30 minutes 3 times a day. Manipulative therapy with special attention to the splanchnic region was given 4 times a day. In order to relieve distention with its accompanying discomfort, paracentesis was performed on December 28, 1943, and 10,500 cc. of clear amber fluid were obtained, the laboratory analysis of which is reported below:

The specimen submitted consisted of approximately 150 cc. of comparatively clear amber fluid. This fluid contained 0.5% of protein with 178 erythrocytes per cu. mm. Smears have been prepared from the sediment of the materials submitted and show predominantly erythrocytes with a few polymorphonuclears and a moderate number of mesothelial cells. We do not demonstrate any aggregates of cells that might lead us to believe that a tumor is present, though there are some signet-ring cells that sometimes point in that direction.

During her stay in the hospital the patient's temperature at no time exceeded 98.6° F., and on the average was about one degree below this level.

Blood counts are reported in table 1. Urinalyses were all essentially negative except for a trace of albumin on December 21, 1943, which was absent on later examinations. During the time it was necessary to discontinue the administration of insulin, blood sugar levels rose to 235 mg. per 100 cc., but were reduced to 153 mg. per 100 cc. when insulin was reinstituted. On December 22, 1943, blood uric acid was 3.7 mg. per 100 cc.

Because of the ascites, and a history of nocturnal dyspnea, consideration was given to the possibility of a moderate degree of left ventricular failure. The patient was digitalized, and given 15 grains of ammonium chloride three times a day. Under this therapy there was no recurrence of the nocturnal dyspnea. The digitalis therapy was continued until the time the patient expired.

Following discharge from the hospital on December 31, 1943, convalescence was again uneventful, and the patient was ambulatory with moderate restriction of activity. However, there was a steady accumula-

### Macroscopy:
Approximately 20 cc. of deep yellow clear fluid were submitted. This fluid has a protein content of 0.75 per cent. A white coagulum formed at the bottom of the tube.

### Microscopy:
Direct examination of some smears of the sediment of the fluid referred to above shows a high protein content with erythrocytes and some lymphocytes. Cells of tumor cannot be identified. Sections of the coagulum from the fluid referred to above show strands of epithelial cells. Tumor elements cannot be demonstrated.

Following paracentesis it was thought that there might be a mass in the lower right quadrant, but survey films of the abdomen obtained September 9, 1944, failed to confirm this. On September 11, infection developed at the site of the paracentesis, but, as indicated by the following x-ray report, was apparently confined to the subcutaneous area. This responded readily to incision, drainage, and irradiation therapy.

Anteroposterior survey films obtained of the abdomen, as requested, are negative for roentgen evidence of intestinal obstruction. Considerable gas prevails within the stomach and right cecocolon, while a notable quantity of fecal material is manifest within the transverse colon and splenic flexure. Multiple ovoid and elliptical shaped shadows, possessing varying degrees of increased radio density, are seen distributed within the colon and as well within the fornix of the gas filled stomach. The distribution and characteristics of the latter opacities indicate that such are in all probability attributable to ingested medication of tablet form. Some enlargement of the liver is indicated and a rather diffuse hazing of abdominal viscera may be accounted for on the basis of residual peritoneal exudate following paracentesis. We are unable to delineate satisfactorily a right lower abdominal mass or neoplasm determined on clinical examination of the abdomen. Abdominal survey films are otherwise negative.
The patient remained about the same clinically until December 16, 1943 when she again complained of obstriction and generalized pain in the abdomen. The abdomen was hard and distended, and both dullness and tympany were elicited on percussion. The patient received manipulative therapy twice daily and 1 cc. of 1 to 2000 prostigmine once daily by hypodermic injection supplemented by oral dosage of prostigmine bromide. The patient, at this time, reported a history of nocturnal dyspnea of four weeks' duration. She was hospitalized on December 20, 1943. Since she was unable to take food by mouth the insulin was temporarily discontinued. Survey films of the abdomen were made which suggested the presence of ascites, but did not indicate the presence of intestinal obstruction.

Treatment instituted consisted of the use of an oral Wangensteen apparatus, a rectal tube, and hot turpentine stupes applied for 30 minutes 3 times a day. Manipulative therapy with special attention to the splanchic region was given 4 times a day. In order to relieve distention with its accompanying discomfort, paracentesis was performed on December 28, 1943, and 10,500 cc. of clear amber fluid were obtained, the laboratory analysis of which is reported below:

The specimen submitted consisted of approximately 150 cc. of comparatively clear amber fluid. This fluid contained 0.5% of protein with 178 erythrocytes per cu. mm. Smears have been prepared from the sediment of the materials submitted and show predominantly erythrocytes with a few polymorphonuclears and a moderate number of mesothelial cells. We do not demonstrate any aggregates of cells that might lead us to believe that a tumor is present, though there are some signet-ring cells that sometimes point in that direction.

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Following discharge from the hospital on December 31, 1943, convalescence was again uneventful, and the patient was ambulatory with moderate restriction of activity. However, there was a steady accumulation of fluid in the abdomen so that it was necessary to perform paracentesis at intervals of approximately five weeks. On each occasion from 8000 to 10,000 cc. of fluid were removed.

In September, 1944, while vacationing at the seashore the patient complained of extreme weakness, and returned home in a very weakened condition. Once again there was considerable abdominal distention, and dullness on percussion. It was felt that paracentesis must be performed again, but in view of her extremely weakened condition, and the danger of shock, she was hospitalized on September 5, 1944. At the time of this admission her weight was 135 pounds, blood pressure was 135 systolic and 80 diastolic, urinalysis negative, and blood count as reported in table 1. The temperature on admission was 100° F., but fell within 24 hours to the subnormal levels observed on previous admissions.

Paracentesis was performed on September 6, 1944, at which time 8,800 cc. of deep yellow fluid were obtained, the laboratory analysis of which follows:

**Macroscopy:** Approximately 20 cc. of deep yellow clear fluid were submitted. This fluid has a protein content of 0.75 per cent. A white coagulum formed at the bottom of the tube.

**Microscopy:** Direct examination of some smears of the sediment of the fluid referred to above shows a higher protein content with erythrocytes and some lymphocytes. Cells of tumor cannot be identified. Sections of the coagulum from the fluid referred to above show strands of epithelial cells. Tumor elements cannot be demonstrated.

Following paracentesis it was thought that there might be a mass in the lower right quadrant, but survey films of the abdomen obtained September 9, 1944, failed to confirm this. On September 11, infection developed at the site of the paracentesis, but, as indicated by the following x-ray report, was apparently confined to the subcutaneous area. This responded readily to incision, drainage, and irradiation therapy.

Anteroposterior survey films obtained of the abdomen, as requested, are negative for roentgen evidence of intestinal obstruction. Considerable gas prevails within the stomach and right cecocolon, while a notable quantity of fecal material is manifest within the transverse colon and splenic flexure. Multiple ovoid and elliptical shaped shadows, possessing varying degrees of increased radio density, are seen distributed within the colon and as well within the fornix of the gas filled stomach. The distribution and characteristics of the latter opacities indicate that such are in all probability attributable to ingested medication of tablet form. Some enlargement of the liver is indicated, and a rather diffuse haziness of abdominal viscera may be accounted for on the basis of residual peritoneal exudate following paracentesis. We are unable to delineate satisfactorily a right lower abdominal mass or neoplasm determined upon clinical examination of the abdomen. Abdominal survey films are otherwise negative.
A supplementary transabdominal film study obtained September 13, 1944, demonstrates modification as to relief of the deep subcutaneous and muscle plane of the mid to lower anterior abdominal wall. In the main the roentgen characteristics indicate the probability of cellulitic pathology, the location of which corresponds to the site of previous paracentesis. Radiation therapy directed to the aforementioned cellulitic pathology was instituted as requested.

The patient was discharged on September 24, 1944, and once more was ambulatory. She continued to lose weight. Following this last emptying of the abdomen it was noted that there was very little tendency to become ascitic for several months. On December 12, 1944, the patient complained of chills and weakness which appeared in mid-afternoon. The patient was advised to stop the morning dosage of protamine zinc insulin and several days later the blood sugar level was checked and found to be 142 mg. per 100 cc. There was no recurrence of the chills and weakness, and in spite of the fact that insulin was not resumed, and all dietary restrictions were removed, blood sugar levels never rose above 152 mg. per 100 cc. during the rest of her life.

On January 11, 1945, at 1:00 A.M. the patient collapsed while going to the bathroom. The writer was called and found her in a mild state of shock, with a temperature of 103.4° F. She complained of abdominal pain. Sedation was administered, and the following morning the temperature was 96.4° F. She was hospitalized. Figure 3 records the temperature and pulse during this fourth stay in the hospital. At this time the patient weighed approximately 110 lbs. The urine was negative, blood count as shown in table 1, plasma protein 4.8, and blood sugar 151 mg. per 100 cc. The patient was given aminoids in an attempt to increase the plasma protein level, but it was necessary to discontinue this medication because it caused nausea and vomiting. The clinical picture suggested the necessity of differentiating a carcinomatous process in the abdomen, possibly liver, and Simmond's cachexia. With this in mind the following laboratory, x-ray, and ophthalmologic findings were obtained.

**Laboratory Findings:**
- September 15, cephalin flocculation, 3+ 3+ 0000
- September 18, icterus index, 4.2
- September 18, van den Bergh indirect, negative
- September 18, blood amylase 62 mg. per 100 cc.
- September 20, blood sugar, 142 mg. per 100 cc.

**X-ray Examination:** Anteroposterior survey film of the abdomen as requested shows gas distributed within the stomach, transverse and descending colon, and as well in the rectosigmoidal segment. No findings which may be interpreted as indicating intestinal obstruction are recorded, while throughout the pelvis there prevails a generalized increase of tissue density, the exact significance of which is indeterminate. The survey film obtained is otherwise negative for findings of definite pathologic character.
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Supplementary posterior and lateral film studies secured of the skull show the contour and density of the calvarium to conform to average normal for a patient of this age period and we are unable to establish osteolytic or pathologic changes of a metastatic neoplastic order. The calcified pineal body shows a very slight shift to the right of the midline though such is not interpreted as of significance, while the sella turcica and clinoid processes show no appreciable alteration as to contour and delineation. The petrous ridge structures appear intact. There is present a developmental absence of the right frontal sinus.

On the basis of abdominal survey film finding, it is suggested that consideration be given to the advisability of direct evaluation of intra-pelvic soft parts.

**Ophtalmologic Report:** Eye ground examination, under mydriasis reveals:

**Right eye:** The crystalline lens shows very mild or early cloudiness, the other dioptric media are clear and transparent. The optic disk is clear in outline and all details are clearly visible. The optic disk is somewhat paler in color than average. The retinal arteries are straighter in course than average and show an increased white reflex. The retinal veins follow the average pattern of course, size, and distribution. The area of macula appears normal. There is no evidence of hemorrhage, exudate or edema.

**Left eye:** The findings here are exactly as recorded above for the right eye. The crystalline lens shows an early cloudiness on oblique illumination. The optic disk is clear and definitely marginated, but possibly paler in color than average.

**Impression:** Minimal changes of arteriosclerosis. No evidence of increased intracranial pressure. Early senile cataract, bilateral. When this patient is able to sit in a chair the visual fields should be plotted. Perimetry may be of assistance in deciding whether or not the disk is physiological.

A recheck of the pelvis revealed senile vaginitis, the lateral regions negative, and the uterus small, hard, and fixed. It was decided in consultation with the Department of Radiology to make x-ray studies of the liver and spleen using thorotrast as a contrast medium. The report of these studies follows:

Hepato-splenography, employing thorotrast as opaque medium was carried out as requested, the patient being seen for repeated examinations following intravenous administrations of thorotrast, on February 10 and again on February 11 and 13, 1945 at which times 24 cc. of thorotrast were administered in 100 cc. normal saline.

Abdominal survey films were secured and showed the liver demonstrated. There was suggested moderate enlargement of the liver. The spleen was also seen in the survey film and showed no frank enlargement. There were no calcifications demonstrated in either the liver or spleen.

Re-examination of the liver and spleen was made February 11, 1945, 24 hours after the first intravenous injection of thorotrast (24 cc.). There appeared to be some increased radio density to the liver and spleen, which was quite homogenous. Re-examination of the liver and spleen was made February 12, 24 hours after the second intravenous injection of 24 cc. of thorotrast. At this time the spleen and liver were definitely increased in radio density throughout, the density being quite homogenous, there being no translucencies within limits of the liver to indicate metastatic neoplasm or liver abscess.

The next film examination was made February 14, following a third and final intravenous injection of thorotrast. Films made at this time showed progressive increase in radio density to the liver and spleen. In each instance the part under examination appeared to be sharply defined in its contour and relief, and in the main the overall thorotrast density appears to be quite homogenous. There were no gross pathologic variations in density of the liver and spleen at this time.

Films obtained February 16, 1945, showed well visualized liver and splenic shadows, increased in radio density throughout, with no findings present to indicate the presence of hepatic metastases of malignant order, and the liver generally showed no radiological eview...
Supplementary posterior and lateral film studies secured of the skull show the contour and density of the calvarium to conform to average normal for a patient of this age period and we are unable to establish osteolytic or pathologic changes of a metastatic neoplastic order. The calcified pineal body shows a very slight shift to the right of the midline though such is not interpreted as of significance, while the sella turcica and clinoid processes show no appreciable alteration as to contour and delineation. The petrous ridge structures appear intact. There is present a developmental absence of the right frontal sinus.

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Abdominal survey films were secured and showed the liver demonstrated. There was suggested moderate enlargement of the liver. The spleen was also seen in the survey film and showed no frank enlargement. There were no calcifications demonstrated in either the liver or spleen.

Re-examination of the liver and spleen was made February 11, 1945, 24 hours after the first intravenous injection of thorotrast (24 cc.). There appeared to be some increased radio density to the liver and spleen, which was quite homogenous. Re-examination of the liver and spleen was made February 12, 24 hours after the second intravenous injection of 24 cc. of thorotrast. At this time the spleen and liver were definitely increased in radio density throughout, the density being quite homogenous, there being no translucencies within limits of the liver to indicate metastatic neoplasm or liver abscess.

The next film examination was made February 14, following a third and final intravenous injection of thorotrast. Films made at this time showed progressive increase in radio density to the liver and spleen. In each instance the part under examination appeared to be sharply defined in its contour and relief, and in the main the overall thorotrast density appears to be quite homogenous. There were no gross pathologic variations in density of the liver and spleen at this time.

Films obtained February 16, 1945, showed well visualized liver and splenic shadows, increased in radio density throughout, with no findings present to indicate the presence of hepatic metastases of malignant order, and the liver generally showed no radiological evi-
ences to support the presence of abscess, cyst or other pathological changes, which might tend to alter the reticulo-endothelial storage of the thorium compound.

The final films made in this case on February 22, 1945, approximately two weeks after the first intravenous injection of thorotrast showed persisting increased radio density to the liver and spleen. There was but little, if any, actual enlargement of the spleen in terms of overall size. The contour of the liver appeared to be smooth and regular. The spleen showed no frank enlargement or variation in radio density by virtue of thorotrast opacity.

The homogeneity of the liver opacity was questioned at this time, in terms of suspicious though not definite rounded radiotranslucency within the central substance of the liver, and alteration in density at the dependent outer limits of the right lobe of the liver. These findings were not sufficiently well defined to warrant opinion of intrahepatic pathology, though the centrally placed defect might well suggest a destructive lesion, possibly of an infective type. There were no findings observed to suggest or indicate the presence of metastatic foci within limits of the liver or spleen, and therefore carcinoma of the liver, either primary or metastatic, would appear to be eliminated on the basis of present findings.

At her own insistence the patient was discharged from the hospital in a semi-ambulatory condition, on February 23, 1945. She was very weak, but had been able to sit in a chair and have bathroom privileges for a week prior to discharge.

In view of the fact that the blood chemistry and x-ray studies did not reveal evidence of liver pathology, it was decided to make a therapeutic test for the possible existence of pituitary cachexia. Accordingly on February 25, 1945, treatment consisting of the daily intramuscular injection of 1 cc. of polyansyn (Armour) was instituted. During the first week of this therapy the patient seemed somewhat stronger, but at 11:30 P.M. on March 4, 1945, while on the bed pan, she suddenly collapsed, and passed into a comatose state that lasted approximately 30 minutes. During this time she was incontinent as to both urine and feces. When the writer saw her at midnight she was semiconscious, had no pain, her blood pressure was 106 systolic and 60 diastolic, her pulse was 80 with a thin, thready quality, and her temperature was 97.4° F. The muscles of the right upper and lower extremities were spastic, reflexes were exaggerated and there was a slight slurring in speech.

The patient was hospitalized immediately. On admission to the hospital urinalysis was essentially negative, and blood count was as reported in table 1. Temperature and pulse during this hospital period are shown in figure 5. Within 3 days the blood pressure had returned to 130 systolic and 80 diastolic and the spasticity on the right side had disappeared. There was, however, considerable abdominal distention with slight discomfort, and on March 8, 1945, 1900 cc. of fluid were removed from the abdomen. There was apparently more fluid present, but it was necessary to discontinue the paracentesis because of the clinical status of the patient. Smears and cultures of this fluid were negative for bacteria. Laboratory analysis was as follows:

This fluid had a relatively low protein content and was comparatively clear. Direct examination of the sedimentation of the fluid shows a considerable percentage of polymorphonuclear leukocytes. A predominance of lymphocytes, a few endothelial cells, but no aggregates of cells suggesting tumor. These findings would suggest a transudate.

Because of lack of clinical improvement the polyansyn was discontinued on March 12. On March 14, the eye grounds were re-examined under mydriasis, with the following findings:

Right eye: The crystalline lens is slightly clouded, the dioptric media otherwise are clear and transparent. The optic disk is plainly seen, sharp in outline and detail, but is paler than normal. The entire retina is paler in color than average. The arteries are small in caliber, straighter than average, and show an increased white reflex. The veins appear normal in course, distribution and caliber. The area of the macula appears normal. No hemorrhage, exudate, or edema is seen.

Left eye: The findings are as above reported for the right eye—cloudiness of the lens, pallor of the disk and retina in general, increased white reflex of the retinal arteries.

Conclusion: The fundi show arteriosclerotic changes, lens opacities (senile), and pallor of the disk and retina. This pallor indicates systemic changes of anemia, rather than specific intraocular pathology. No evidence of increased intracranial pressure can be found. Recheck examination of the fundi on March 28, 1945, shows the same general findings as above described, except that the appearance of pallor of the disks and retinae is more pronounced.

In view of the retinal indications of anemia, the blood count was re-checked on March 15 as reported in table 1, at which time the hematocrit reading was 28 per cent, and the reticulocyte count 0.5 per cent. At this time her blood sugar was 128 mg. per 100 cc., blood chloride 533 mg. per 100 cc. and plasma protein 5.78 mg. per 100 cc.

The abdomen had meanwhile become quite distended and there was a decrease in fecal and urinary output. It was felt that paracentesis must again be attempted, but in view of the relative anemia revealed by the low hematocrit reading it was decided to give a transfusion of 500 cc. of whole blood first. This was started on March 16 at about 2:30 P.M. At 4:00 P.M. after receiving 300 cc. the patient went into shock. Blood pressure was 80 systolic and 40 diastolic. The shock was treated with heat to the extremities, elastic bandages on the lower extremities, eleva-
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tion of the foot of the bed, 3 minims of neosynephrin subcutaneously, and continuous upper dorsal soft tissue manipulation. It was necessary to discontinue the elevation of the foot of the bed because of the embarrassment to respiration caused by the fluid in the abdomen pressing against the diaphragm. The blood pressure gradually rose to 120 systolic and 75 diastolic. When the patient complained of right flank pain consideration was given to the possibility of renal infarction. A catheterized specimen of urine taken at 12 midnight showed a one plus reaction to albumin with occasional pus cell. It was otherwise negative including a benzidine reaction for blood.

On March 17, the patient was sufficiently recovered to permit para
centesis, and 2400 cc. of fluid were removed. This fluid was similar to that removed on previous occasions. It had a protein content of 4.5 per cent, with 10 to 15 red cells, and 3 to 5 white blood cells per high power field. There was a negative van den Bergh reaction.

At this time a small mass approximately 1 cm. in diameter was ob­
erved in the right breast. It was rounded, firm, the skin was not ad-
herent, there was no dimpling of the skin, and no nipple retraction. There were no palpable lymph nodes in the axillary, suprACLavicular, or intra-
clavicular areas. This mass had not been observed on previous examina-
tions, and the patient when questioned, reported that she had never noticed it.

Urinary output continued small, and on March 19 the blood urea nitrogen level was 42 mg. per 100 cc. Fluids were forced and a re-
check made on March 25, at which time the blood urea nitrogen level was 63 mg. per 100 cc. Fluids by mouth were supplemented by 250 cc. of saline with 5 per cent glucose given intravenously on March 26, and 500 cc. on March 27, and 28. Fifteen grains of diuretin were given three times daily. Nausea and vomiting which occurred during intravenous administration, was partially controlled by 50 mg. of pyridoxine hydrochloride plus 50 mg. of thiamine chloride given intra-
venously. Gaseous distention was controlled by the use of a rectal tube, and intramuscular injections of 1 to 2000 prostigmine hydrochloride. Blood urea nitrogen, on March 28, was 47.6 mg. per 100 cc. and on March 30 was 53.2 mg. per 100 cc.

The ammonium chloride was discontinued on March 24. Blood chloride level on March 28 was 516 mg. per 100 cc. The patient was now semicomatose. It was necessary to employ a rectal Wangensteen appar­atus and catheterization, and to give 500 cc. of saline intravenously daily.

In view of the low chloride level, low plasma protein, and high blood urea, it was decided to institute therapy for addisonian crisis. On April 4, the patient received 20 mg. of desoxycorticosterone acetate intramuscularly, and 1000 cc. of 15 per cent sodium chloride with 10 per cent glucose, plus 10 cc. of adrenal cortex extract intravenously. The clinical response was rather dramatic. The patient regained consciousness, took liquid and soft food by mouth, and the pulse rate dropped as indicated in figure 5. The blood chloride level on April 5 was 556 mg. per 100 cc. On this date she received 1000 cc. of physiological saline with 10 per cent glucose, and 15 mg. of desoxycorticosterone acetate intramuscularly. She seemed stronger, and for the first time in ten days requested food and asked for permission to sit on the side of the bed.

At 4:30 in the afternoon of April 5, while expelling an enema, the patient suddenly expired.

Autopsy No. A-45-375
Died: April 5, 1945
Autopsy: 4/6/45

The body was that of an emaciated, senile, white female said to be 69 years old. The body length was 64 inches and her weight was estimated at 80 pounds. The scalp was fairly well covered with gray hair. The pupils were equal in size. A tumor mass was found in the right breast. This tumor lay deep on the pectoral muscles. It was firm to the touch, somewhat
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irregular in outline, and the cut surface presented sharp edges with the mottled steel gray appearance characteristic of carcinoma. This mass measured 5 x 2 cm. and showed itself microscopically to represent scirrhous carcinoma of the breast.

The abdomen was distended and showed a number of areas where paracentesis had been performed. A total of 6,950 cc. of serofibrinous fluid were recovered from the abdominal cavity. The subcutaneous fat was negligible.

The pericardial sac contained 75 cc. of turbid fluid. The heart measured 13.5 x 10 x 6 cm. The greatest diameter of the thorax at the upper level of the diaphragm was 24 cm. providing a cardiothoracic ratio of 13.5/24. The heart weighed 380 grams. The mitral valve was distorted, evidencing chronic mitral valvulitis. All the chambers of the heart were greatly dilated, and large clots had formed within the chambers. Arteriosclerosis of the coronary system was excessive, and the anterior descending limb of the left coronary artery was particularly involved.

The pleural cavity showed an abundance of adhesions throughout all portions. The lungs weighed respectively, right and left, 330 and 370 gm. These lungs were edematous and each showed reinfec tion lesions of tuberculosis in each apex. Thrombi were found in the smaller pulmonary vessels and there was considerable exudate in the bronchial tree.

The esophagus presented no noteworthy lesions.

The stomach was empty and presented no noteworthy lesions.

The pancreas presented evidences of atrophy.

The spleen measured 11 x 8 x 3 cm., weighed 180 grams, and presented no noteworthy changes.

The liver was 17 cm. tall and weighed 1540 gm. Multiple abscesses were found throughout the liver containing greenish yellow pus, giving one the impression of abscesses about the bile ducts. This pus presented the presence of colon bacilli.

The internal genitalia presented the characteristic changes of atrophy.

The urinary bladder was empty.

The left ureter was obstructed with resulting pyelactasis. Some pyelactasis was demonstrated on the right side also.

The left kidney measured 13 x 7 x 4 cm. and weighed 200 gm. The right kidney measured 12 x 6 x 3 cm. and weighed 240 gm. These kidneys were somewhat softened, and gave the impression of urinary sepsis.

The right suprarenal gland presented no noteworthy changes.

The left suprarenal gland showed autolysis about the medullary substance, the cortical substance was scant.

The cranium presented no evidences of fracture, but there was some thickening and some condensation of the cranial bone.

The brain presented some distention of the lateral ventricle, and some adhesions were demonstrated about the base of the brain. Adhesions were demonstrated about the left lobe of the cerebellum.

Sclerosis of the circle of Willis was demonstrated extending into the vessels on the right side.

The pituitary gland was of average size but somewhat mottled in color, one portion suggesting the presence of an area of softening, or perhaps tubercle formation.

Microscopy:

Sections of the pituitary show considerable edema and considerable fibrous overgrowth in the stroma. We do not demonstrate evidence of tumor or evidence of specific infection. Some cystic changes are demonstrated about one margin.

Sections of the heart muscles show areas of atrophy of the muscle fibers. These sections do not demonstrate to good advantage the areas of scarification.

Sections of the lungs show widespread pulmonary edema with considerable mucoid and watery exudation into the bronchial tree. We do not demonstrate evidences of tumor.

Sections of the tumor from the mammary gland show it to present excessively dense, somewhat hyalinized supporting stroma. Between the stromal elements strands of completely anaplastic epithelial cells can be demonstrated. In some areas these strands are narrow, one and two cells in width, in other areas there are larger aggregates of cells resembling the comedo carcinoma. Ductal hyperplasia is demonstrated in some areas. Invasion of the fat about the tumor is quite evident.

Sections of the intestines present no intrinsic lesions. Uniformly throughout, however, these sections show tumor masses composed of cells identical to those described in the breast, and these tumors are located uniformly in the serosa, and invading the muscularis propria.

Sections of fragments of peritoneum showing the studding of small tubercle-like bodies show these lesions also to represent possible metastatic tumors identical in cellular architecture with the tumor described in the mammary gland.

Sections of the liver show large areas of abscessed formations with here and there some staining with bile. These abscesses contain purulent and necrotic debris. A few giant cells can be demonstrated about the margins of the abscesses. It would be our impression that these abscesses are cholangitic. The liver substance is distorted by the presence of the abscesses which show congestion with pigmentation.

Sections of the spleen show some congestion, and an excess of polymorphonuclear leukocytes. There is some thickening of the stroma.

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Sections of the spleen show some congestion, and an excess of polymorphonuclear leukocytes. There is some thickening of the stroma.

Sections of the suprarenal glands present no noteworthy changes.
Sections of the kidneys show very frank evidence of suppurative disease. The tubules are distended with pus, and the supporting framework shows suppurative changes. Suppuration is most marked as the pelvic portions are approached.

**Anatomical Diagnosis:**
- Scirrhous carcinoma of the mammary gland
- Carcinoma simplex, Broders' grade IV, of the mammary gland
- Coronary atherosclerosis
- Dilation of the heart
- Pulmonary edema
- Abdominal carcinomatosis
- Urinary sepsis

**Cause of Death:**
- Immediate: Abdominal carcinomatosis
- Contributory: Coronary occlusive disease

**Discussion**

This case poses many questions for consideration by the internist, pathologist, biochemist and radiologist. Some of the autopsy findings fit into the clinical picture, and answer questions which had us perplexed during the clinical management of this case. On the other hand, some of the autopsy findings do not, even in retrospect, permit one to fit them into typical clinical pictures of the conditions reported.

The spontaneous remission of the diabetic syndrome posed a question which was difficult to answer completely during the life of the patient. However, the apparent alteration in the temperature control mechanism, and the cachexia in the absence of proven malignancy, made one suspicious of pituitary-hypothalamic dysfunction with the possibility of the patient having the physiological status similar to that of the Houssay phenomenon. This was to a certain degree confirmed by the autopsy findings in the pituitary gland. On the other hand a similar state may exist when there is diminished functional activity of the adrenal cortex. During the latter part of the clinical management of this case there was evidence of adrenal cortex deficiency manifested by the changes noted in blood concentration, blood chloride, plasma protein, and blood urea levels, as well as by the rather dramatic response to treatment instituted for addisonian crisis.

There are several questions yet to be answered in regard to the carcinomatosis of the intestines and its similarity in microscopic architecture to the breast mass. If the breast mass was primary, and existed during the rather lengthy duration of the patient's illness, why was there no adherence to the skin, and no demonstrable lymphatic involvement? The increase in sedimentation rate and the cachexia present were strongly suggestive of carcinoma, but why in the many radiographic studies and surveys did we not find more evidence of the marked changes in the intestines observed at autopsy? If the breast mass was primary, why and how was there metastasis to the intestines without involvement of the pleura, lungs, liver or bone? We might answer that by saying it was blood borne, but again, as we consider the vascular anatomy, why to the intestines? One other question regarding this phase of the case: Why, in spite of frequent analysis of the ascitic fluid, was there no microscopic evidence of tumor cells, or cells suggestive of tumor?

The finding of the multiple liver abscesses was not only surprising, but leaves several questions to be answered. It has been suggested that they may have been a result of the altered anatomy following the production of the choledochoepiploic fistula. If so, why were they not demonstrated immediately in the thorotrust studies? Where, at any place in the clinical studies, are there presented the fever and leukocytosis considered to be important diagnostic criteria of this condition? At no time was there any marked leukocytosis except that immediately following the cerebral accident, and the temperature, as is evidenced in figure 3 and figure 5, was markedly subnormal for the greater part of the clinical course. The change in the blood amylase level was suggestive of progressive liver dysfunction. However, at no time did the van den Bergh test, icterus index, or cephalin flocculation test yield results in keeping with the degree of involvement found at autopsy. Furthermore, if these liver abscesses were cholangitic why was there no jaundice?

The autopsy findings do, to a certain degree, justify the clinical impressions of pituitary cachexia and Addison's disease contributing to the latter part of the clinical course, but the clinical picture as a whole remains unclear.

**NOTE:** Readers of OSTEOPATHIC MEDICINE are invited to contribute further discussion of this case.—EDITOR.
Sections of the kidneys show very frank evidence of suppurative disease. The tubules are distended with pus, and the supporting framework shows suppurative changes. Suppuration is most marked as the pelvic portions are approached.

**Anatomical Diagnosis:**
- Scirrhous carcinoma of the mammary gland
- Carcinoma simplex, Broders' grade IV, of the mammary gland
- Coronary atherosclerosis
- Dilation of the heart
- Pulmonary edema
- Abdominal carcinomatosis
- Urinary sepsis

**Cause of Death:**
- Immediate: Abdominal carcinomatosis
- Contributory: Coronary occlusive disease

**Discussion**
This case poses many questions for consideration by the internist, pathologist, biochemist, and radiologist. Some of the autopsy findings fit into the clinical picture, and answer questions which had us perplexed during the clinical management of this case. On the other hand, some of the autopsy findings do not, even in retrospect, permit one to fit them into typical clinical pictures of the conditions reported.

The spontaneous remission of the diabetic syndrome posed a question which was difficult to answer completely during the life of the patient. However, the apparent alteration in the temperature control mechanism, and the cachexia in the absence of proven malignancy, made one suspicious of pituitary-hypothalamic dysfunction with the possibility of the patient having the physiological status similar to that of the Houssay phenomenon. This was to a certain degree confirmed by the autopsy findings in the pituitary gland. On the other hand, a similar state may exist when there is diminished functional activity of the adrenal cortex. During the latter part of the clinical course, and the temperature, as is evidenced in figure 3 and figure 5, was markedly subnormal for the greater part of the clinical course. The change in the blood amylase level was suggestive of progressive liver dysfunction. However, at no time did the van den Bergh test, icterus index, or cephalin flocculation test yield results in keeping with the degree of involvement found at autopsy.

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THE TOXEMIAS OF PREGNANCY: A WORKING HYPOTHESIS

Julian L. Mines, III

and

Olwen C. Forbes

Introduction

Eclampsia has long been referred to as “the disease of theories.” Its cause has been attributed to dysfunction of the liver, kidney, placenta, endocrine system, and to bacterial infection, etc. Dexter et al., state that it is apparent, however, that the toxemia is not due primarily to uremia, liver insufficiency, hypoglycemia, electrolyte imbalance, hypocalcemia, guanidine intoxication, pyelonephritis, hypothryoidism, overactivity of the posterior pituitary gland, or hypoproteinemina. Conclusive evidence is still lacking that a specific toxin is responsible for the production of these toxemias.

Purpose

The purpose of this paper is threefold. It is to present an hypothesis to account for the toxemias of pregnancy, to suggest a rational procedure for their prevention and management, and to stimulate further research by clinicians, physiologists, and biochemists which will both reduce the area of the unknown, and will evaluate the hypothesis offered.

The simplest statement of our hypothesis is this: the toxemias of pregnancy are not disease entities, but are conditions or processes which result from altered metabolism of the pregnant organism. What do we mean by this statement? We shall try to make our point by considering the metabolic functions of the pregnant organism as a whole, of certain organs and systems which have known clinical relation to pregnancy, and by analyzing the effect of certain specific dietary components on their metabolic functions.

But first a more general statement of assumptions must be made in order to establish the base on which our hypothesis is constructed. Our first assumption is that optimal metabolism by the pregnant organism, as by any organism, is dependent upon adequate nutrition. The diet must make available needed quantities of essential dietary components, and there must be adequate utilization of ingested food. Adequate utilization is in turn dependent on satisfactory functional levels of the maternal assimilative, detoxifying, excretory, endocrine, and reproductive organs.

In order to limit the field of discussion in this paper, our second assumption is that the functional level of these organs and systems is adequate prior to pregnancy. Under these restricted conditions our hypothesis now states that the toxemias of pregnancy result from nutritional inade-
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idoacetic acid, with an accompanying decrease in creatine synthesis. The accumulation of guanidoacetic acid may further add to fatty changes in the liver. This is so because the small amount of methyl groups available for the synthesis of creatine is lost, as far as other transmethylation processes are concerned, since the synthesis of creatine from guanidoacetic acid and labile methyl groups, is an irreversible process.\textsuperscript{7} The accumulation of guanidoacetic acid may prove to have a direct bearing on the production of the eclamptic seizures because creatine synthesis is decreased, and this substance is necessary for normal muscular activity.\textsuperscript{14}

Sulfhydryl Groups

The sulfhydryl content of cystine and methionine may prove to be of paramount importance, for these two substances are the only sources of sulfur for the synthesis of the body sulfoproteins, and such compounds as thiocyanate, taurocholic acid, ergothioneine, glutathione and fibroid proteins, particularly fibrinogen.\textsuperscript{15} Cell respiration, antitoxin formation, and detoxification in general are all dependent in some degree on the sulfhydryl groups.\textsuperscript{8} An important recent development has been the discovery that the oxidation-reduction states may be a controlling factor in the kinetics of certain enzymatic processes, and there are strong indications that the sulfhydryl groups are involved in these processes.\textsuperscript{16}

The role of the sulfhydryls in enzymatic activity has been investigated recently by Barron and Singer.\textsuperscript{17} They concluded that the following enzymes participating in carbohydrate, fat, and protein metabolism, are sulfhydryl enzymes: in the first phase of carbohydrate metabolism (glycogen to pyruvate), muscle phosphorylase, phosphoglucomutase, hexokinase, and phosphoglyceraldehyde-oxidase are all sulfhydryl enzymes. In the second phase (pyruvate to lactate, or pyruvate to acetaldehyde plus carbon dioxide), carboxylase, the enzyme leading to alcohol fermentation, is a sulfhydryl enzyme. Enzymes leading to lactic acid formation are not.

In fat metabolism, liver stearate oxidase, B coli stearate, and oleate oxidase, B-hydroxybutyric dehydrogenase, acetate-oxidase, and pancreatic lipase, are sulfhydryl enzymes.

In protein metabolism, d-amino oxidase, transaminase, 1-glutamic dehydrogenase, and monamine oxidase are sulfhydryl enzymes.

A pregnant organism must function at optimal levels to maintain the integrity of pregnancy. Toxic metabolites resulting from aberrations in the metabolism of carbohydrate, protein and fat, may be expected to depress the level of function. Therefore, in view of the observations on the importance of sulfhydryl containing enzymes in the optimal metabolism of carbohydrate, protein, and fat, it is evident that sulfhydryl containing enzymes are important to our consideration of the toxemias of pregnancy.

So far we have discussed the dietary components choline, methionine, and cystine as they affect metabolism in general. We will now consider how they affect the function of certain organs and systems which have known clinical relations to pregnancy.

Liver

Because the eclamptic liver can only be studied at autopsy, the pathologic changes taking place within this organ before fatal toxemia occurs must be postulated. We are inclined to agree with Delafield and Prudden\textsuperscript{19} that the liver of the eclamptic first shows a necrosis and degeneration resulting from toxic substances produced either by bacterial infection or faulty cell metabolism, and that then there is more or less pronounced autolysis produced by the ferments resident in the liver cells. The fatal nature of the disease is probably dependent more upon the destruction of
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Fig. 1. Diagram of Liver Lobule.
the liver cells than upon the exogenous inciting infection or toxemia. It has been suggested that the necrosis of the liver cells is a precursor of hemorrhage. If the lipotropic factors choline and methionine are markedly deficient, it seems reasonable that the capacity of the liver for storing glycogen will be interfered with. The glycogen content of the liver cells will be replaced by neutral fats, cholesterol and phospholipids. Thus, there results an interference with the normal metabolic processes of the liver cells.

We believe that alterations in the metabolic processes requiring sulfhydryl compounds may be responsible for some of the liver pathology of the toxemias, particularly in relation to (1) fibrinogen, (2) detoxification, (3) enzyme activity, and (4) glutathione.

The physiologists state that in normal individuals proteins are absorbed from the duodenum and jejunum as amino acids. However, it is true that incompletely digested proteins (e.g. egg albumin) can be absorbed from the small intestine as well. Dieckmann has suggested that the toxemic patients have a decreased amount of proteolytic enzymes. We would further this view in as much as pancreatic lipase and some proteolytic enzymes require —SH groups for their integrity, and a deficiency of these essential compounds may more readily permit the absorption of incompletely digested proteins. In the presence of inadequate amounts of sulfur, the failure to detoxify indole and skatole in the liver may add further embarrassment to the liver. The incompletely digested protein may be shunted directly to the right lobe of the liver as proven by studies on the streamlining of blood flow within the portal vein (fig. 2). Such a mechanism might explain the predominance of right lobe liver pathology, as well as the generalized hepatic pathologic change observed in toxemia. In the normal individual these incompletely digested proteins would be converted to amino acids by enzyme activity (some —SH containing enzymes being essential for this mechanism). In as much as excess amino acids are not stored in the body, they will be denitrogenized in part, and some converted to glycogen and fat. If a deficiency of pyridoxine is associated with toxemia, the excess amino acids will not be converted to glycogen and fat, but will accumulate in the right lobe of the liver particularly, to be retained as toxic metabolites.

In a patient whose diet is deficient in methionine and cystine there might result a deficiency of the sulfhydryl enzymes permitting an aberration of protein metabolism, leading to an overwhelming accumulation of split protein products, which are toxic to body tissues.

Hemorrhage

The liver in eclampsia shows evidence of both focal and massive hemorrhage. The focal hemorrhage probably occurs as a result of varying degrees of liver necrosis. In the physiologic attempt to control the bleeding areas, the liver will increase the production of fibrinogen, even at the expense of depleting other compounds of their sulfhydryl groups.

Fig. 2. Above: Streamlining of Blood Flow Within the Portal Vein. Below: Autolytic Substances being Liberated into General Circulation from Friable Chorionic Tissue.
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creased blood fibrinogen levels of eclamptic patients might be explained by this attempt to control focal hemorrhage. Much of the massive hemorrhage probably occurs during the moribund state. This may be accounted for by the fact that the last function lost by the failing liver is its ability to combat hemorrhagic processes within the body by the production of fibrinogen.

The confusion existing in the minds of pathologists concerning the variations in the severity of the liver lesion is understandable. In as much as glycogen is known to be protective to the liver, the degree of liver pathology will be directly related to the dietary intake during pregnancy. The woman whose diet is high in carbohydrate, low in fat, and deficient in choline, methionine, and cystine will probably show less susceptibility to liver pathology, than the patient whose diet is low in carbohydrate, relatively rich in fat with a deficiency of choline, methionine, and cystine.

Kidney

It appears that the renal pathology seen in the eclamptic state is secondary to the liver changes, and that the kidney lesion of itself is in all probability insufficient to cause death. It is conceivable, however, that the kidney may be the first organ to show the effects of deficiencies of choline and methionine, particularly in patients having low grade urological infections, or a low kidney reserve.

A significant action of choline, perhaps referable to methylation processes, is its function in neutralizing an excess amount of pressor substance from the posterior pituitary lobe. It has been found that the toxemic patient shows a higher titre of blood pressor substance than the normal pregnant patient. Failure to neutralize the excess pressor substance may then result in the production of renal ischemia, thence leading to oliguria. The relative excess of the posterior pituitary pressor substance is due to the failure of its destruction by the liver, or its neutralization by some substance in the blood. This neutralizing principle might well be choline. In true eclampsia, caudal analgesia brings about a marked drop in blood pressure, sometimes as much as 100 mm. of mercury, the urinary output is sometimes increased as much as threefold, the patient becomes rational, and convulsions cease.

Placenta

Several observers have suggested that the hypercholesteremia manifested by toxemic patients has not received the attention it deserves. We believe that hypercholesteremia is of paramount importance in explaining the pathology of the placenta in the toxemic patient. We base this belief on the following considerations.

It has been established that any tissue undergoing increased activity will have an increased cholesterol content, that hypercholesteremia accom-panies a deficiency of choline and methionine, and that cholesterol plays an important role in the production of arteriosclerotic pathology.

It has been suggested that the placental infarcts of toxemia are due either to (a) gradual interruption in the circulation of the placental vessels from physiologic endarteritis, or to (b), abrupt interference in the circulation as the result of rupture, thrombosis, or embolism brought about by trauma caused by fetal movement. Infarction is followed by necrosis and autolysis of the affected tissue. As a result, split protein products such as peptones, histamine, tyramine, guanidine, etc., are liberated by the action of the proteases which are present in all cells. In the third trimester the placenta is becoming senile, and is thus more susceptible to the effects of abnormal physiology, and also normally contains increased amounts of cholesterol. If its cholesterol content is further increased by hypercholesteremia, it is plausible that an excessive deposit of cholesterol in the vicinity of placental vascular structures, coupled with vigorous fetal movements, is responsible for the primary placental endarteritis. This progresses further to local hemorrhage, infarction, and tissue autolysis, with subsequent liberation of increasing amounts of toxic substances (fig. 2). It is another case of an organ whose functional capacity is being impaired, and is itself contributing to the toxic picture. The diversity of tissue autolytic products would seem to exclude the probability of a specific placental toxin.

Up to this point no attempt has been made to rationalize the increased frequency of toxemia in multiple pregnancy, primiparity, and polyhydramnios. Taking these collectively, it is suggested that the underlying common factor of increased intra-abdominal pressure may, by back pressure through the portal circulation, produce varying degrees of liver congestion, and so interfere with its functional capacity. In multiple pregnancy there is also an increased requirement for the "body building blocks," the amino acids. We believe this increased need is met too infrequently in the diet.

The symptomatology of the progressing preeclamptic (vertigo, visual scotomata, pulmonary edema, cerebral edema, etc.) is directly referable to the gradually developing overwhelming accumulation of toxins which, as we have shown, may arise in the liver itself, the poorly functioning kidney, and the placenta.

Endocrine System

During the toxemias of pregnancy there is a relative decrease of estrogen and progesterone, and an increase of chorionic gonadotropin in the blood and urine. The mechanism which accounts for these findings has not been clarified to date, but we believe that glutathione, one of the sulfhydryl compounds, is of great interest in this connection. Glutathione is present in all cells of the body, and is intimately related to oxidation processes within the cells, as well as with intracellular detoxifying processes.
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The two steps involved in this phenomenon are best accounted for tissue, and suddenly be released into intercellular spaces as edema fluid. It has much to do with the production of edema fluid causing pitting edema.

There are two mechanisms which may bring about the sudden release of this water as free fluid causing pitting edema. It can be achieved when the critical level of plasma proteins is reached, or by sudden adrenal cortical insufficiency. The level of circulating blood plasma proteins may be affected by the dietary protein intake, the ability of the liver to synthesize serum albumin and serum globulin, or the loss of protein from the blood stream via poorly functioning kidneys. A sudden adrenal cortical insufficiency due to aberrant sterol metabolism would result in an accumulation of sodium in tissue spaces. There would then be alterations in osmotic balance between intra- and extracellular fluid due to the obligatory extracellular position of sodium. Water would leave the cells, and enter the tissue spaces in an attempt to restore osmotic balance. The result is pitting edema. In addition, the role of increased capillary permeability in the production of edema will be greatly influenced by the circulating toxins present, and by the ability of the circulating erythrocytes to transport oxygen.

Oxygen Transport

The ability of the erythrocytes to transport oxygen is known to be abnormal in cases of toxemia. The following factors may singly or collectively affect the oxygen carrying power of the erythrocytes, and the normal release of oxygen to the tissues. (1) Deficiencies of the proteins and lipids necessary for the production of normal stroma within the erythrocyte (the method by which the hemoglobin is transported in the cell). (2) In specific protein depletion, there may be a lack of an erythrocyte maturing factor, functioning in the liver, and this may in turn lead to the production of immature, nucleated erythrocytes which are poor carriers of oxygen. (3) With toxemia, there is an actual decrease in the number of circulating erythrocytes. This may be the result of inadequate stroma leading to an increased fragility and excessive rate of cell destruction. (4) The relative acidity of the blood stream associated with toxemias would influence the oxygen transmission. (5) Although the function of ergothioneine is unknown, we believe that deficiencies of this compound may interfere with the normal release of oxygen to the tissues.

Nervous Physiology

There is no satisfactory explanation for the increased neuromuscular irritability observed in the fulminating toxemias of pregnancy. We offer the following considerations as being worthy of further study.
The principal role of glutathione in cellular systems is that of continuous reactivation of the sulphydryl enzymes. However, the degree of activity of these enzymes is determined by the oxidation-reduction potential of the cells, that is, by the concentration of glutathione, ascorbic acid, oxidizing agents, hydrogen ion, etc. It has been found that glutathione, in conjunction with ascorbic acid, slowly inactivates chorionic gonadotropin. The relative excess of chorionic gonadotropin observed may be explained by the failure to neutralize it, because of a deficiency of glutathione and ascorbic acid in the cells.

We may now theorize along two different lines to explain the relative decrease in estrogen and progesterone.

The first theory postulates that the placenta is intrinsically able to synthesize estrogen and progesterone, but that synthesis is depressed. If we assume that cystine reduces the disulfide linkage in the gonadotropic glycoprotein, and that glutathione with ascorbic acid inactivates it slowly, then we can postulate that deficiencies of these compounds account for the accumulation of a relative excess of chorionic gonadotropin which in turn suppresses the production of estrogen and progesterone.

An alternative theory postulates that there is a failure on the part of the placenta to synthesize estrogen and progesterone, because of aberrations in sterol metabolism. On this assumption it matters little whether cholesterol and estrogen are derived from a parent sterol, or whether estrogens are themselves derived from cholesterol as such. In either case, the synthesis is a result of a series of oxidation, reduction, and demethylation steps. In as much as choline and methionine are essential for the formation of the compounds necessary to these steps, it is assumed that deficiencies in these substances influence the synthesis of estrogen and progesterone.

Water Balance

Obstetrical patients frequently show a rapid gain in weight with no pitting edema, and then within a short time extensive edema can be demonstrated. Apparently water can be bound in liver, muscle, and connective tissue, and suddenly be released into intercellular spaces as edema fluid. The two steps involved in this phenomenon are best accounted for separately.

Lecithin, a phospholipid, was found to enhance greatly the water imbibing power of gelatin which has colloidal properties similar to those of body tissues. On the other hand, cholesterol diminishes this power. It was believed, therefore, that a tissue with a high phospholipid-cholesterol ratio would imbibe a great deal of water. In general, there is a close relation between the free cholesterol and phospholipids, if one is increased a rise in the other follows closely. This is true in toxemias, as well as in normal pregnancy to a less degree. It is believed that the ratio has much to do with the water balance of the body. An important property of cholesterol is its ability to confer, on a fat or oil, the capacity to absorb relatively larger quantities of water. The water absorbing ability is no doubt due to its tendency to form water in oil emulsions. Therefore seems likely that the increased cholesterol-phospholipid ratio exhibited by toxemic patients binds excessive amounts of water in the fatty tissue of the liver, muscle, and connective tissue, and that this accounts for the rapid gain in weight due to positive water balance without pitting edema.

There are two mechanisms which may bring about the sudden release of this water as free fluid causing pitting edema. It can be achieved when the critical level of plasma proteins is reached, or by sudden adrenal cortical insufficiency. The level of circulating blood plasma proteins may be affected by the dietary protein intake, the ability of the liver to synthesize serum albumin and serum globulin, or the loss of protein from the blood stream via poorly functioning kidneys. A sudden adrenal cortical insufficiency due to aberrant sterol metabolism would result in an accumulation of sodium in tissue spaces. There would then be alterations in osmotic balance between intra- and extracellular fluid due to the obligatory extracellular position of sodium. Water would leave the cells, and enter the tissue spaces in an attempt to restore osmotic balance. The result is pitting edema. In addition, the role of increased capillary permeability in the production of edema will be greatly influenced by the circulating toxins present, and by the ability of the circulating erythrocytes to transport oxygen.

Oxygen Transport

The ability of the erythrocytes to transport oxygen is known to be abnormal in cases of toxemia. The following factors may singly or collectively affect the oxygen carrying power of the erythrocytes, and the normal release of oxygen to the tissues. (1) Deficiencies of the proteins and lipids necessary for the production of normal stroma within the erythrocyte (the method by which the hemoglobin is transported in the cell). In specific protein depletion, there may be a lack of an erythrocyte maturing factor, functioning in the liver, and this may in turn lead to the production of immature, nucleated erythrocytes which are poor carriers of oxygen. (3) With toxemia, there is an actual decrease in the number of circulating erythrocytes. This may be the result of inadequate stroma leading to an increased fragility and excessive rate of cell destruction. (4) The relative acidity of the blood stream associated with toxemias would influence the oxygen transmission. Although the function of ergothionine is unknown, we believe that deficiencies of this compound may interfere with the normal release of oxygen to the tissues.

Nervous Physiology

There is no satisfactory explanation for the increased neuromuscular irritability observed in the fulminating toxemias of pregnancy. We offer the following considerations as being worthy of further study.
There may be a calcium deficiency. Calcium both stabilizes the resting potential of the axones, and calcium as well as magnesium in the muscles acts as an activator for the enzymatic splitting of phosphate from adenosine triphosphate by myosin. Even with adequate intake, a calcium deficiency is entirely possible because the absorption of non-diffusible calcium from the intestinal tract, and its transmission in the bloodstream, is a function of the protein intake, and of the blood plasma level. Therefore, in cases of hypoproteinemia there may be an associated lowering of the serum non-diffusible calcium.

A second consideration which may account for increased neuromuscular irritability involves the possible role of choline in the formation of acetylcholine, and the splitting of acetylcholine by cholinesterase. There has been extracted from rat brain an enzyme, choline acetylase. In the presence of adenosine triphosphate under strictly anaerobic conditions, choline acetylase synthesized acetylcholine in free cell solution. This synthesis requires active sulfhydryl groups, the presence of potassium ions, and an amino group. It is further possible that the rapid splitting of acetylcholine by cholinesterase at the nerve synapse, requires the presence of sulfhydryl containing glutathione. If so, lack of sulfhydryl compounds at the synapse may so prolong the action of acetylcholine that any stimulus may initiate general convulsive seizures.

In view of the foregoing we believe that even in the absence of toxic accumulations of guanidine (from tissue autolysis), and in the presence of adequate amounts of calcium, a deficiency of sulfhydryl containing enzymes can account for the increased neuromuscular irritability observed in fulminating toxemia of pregnancy.

**Vitamins**

The interrelationship between the action of vitamins and choline, methionine, and cystine, as they are concerned with oxidation, reduction, and methylation, seems quite important to us. Apparently a well balanced vitamin intake is just as essential to the well being of both mother and fetus as is a sufficient intake of choline, methionine, and cystine. Certain vitamins are essential in the diet, but, to perform their necessary functions, they require the complementary action of all the other vitamins. This is comparable to the case of the essential amino acids which carry out their function better in the presence of non-essential amino acids. The possible mechanism of certain vitamins known to be essential to the prevention of the toxemias of pregnancy will now be discussed.

Thiamin is intimately concerned with carbohydrate metabolism. Thiamin deficiency results in improper oxidation of carbohydrate, leading to an accumulation of lactic and pyruvic acid, and methyl glyoxol. Since pyridoxine is concerned with the conversion of some of the excess protein to glycogen and fat, pyridoxine insufficiency, coupled with high protein diets, might result in the accumulation of intermediate metabolites in the liver. This mechanism may be an important factor in the production of hyperemesis gravidarum.

There also seems to exist a synergistic action between the lipotropic action of choline and pyridoxine as well as with other components of the B complex. The prolonged feeding of rats on a diet containing adequate choline, but deficient in pyridoxine, resulted in fatty livers.

“Dietary deficiencies of only the heat stable fractions of vitamin B complex produces, in rats, a significant and persistent rise in blood pressure which can be reversed on restoring this factor to the diet. These findings seem to show that some types of hypertension may be metabolic in origin, the cause being perhaps a diminished oxidative activity of the kidney.” In as much as the preeclamptic syndrome is usually accompanied by anorexia and a deficient intake of vitamin B, this may also be a contributory factor to the hypertensive picture.

It is thought that the transport of hydrogen from the products of metabolism to other carriers of molecular oxygen is effected by vitamin C. Its deficiency results in a decreased oxygen utilization. Also, as we have stated previously, glutathione and ascorbic acid acting together, inactivate choric acid and ascorbic acid acting together, inactivate chorionic gonadotropin, as does cystine.

Recent experimental work tends to indicate that vitamin K seems to have a definite effect upon blood clotting, probably through an oxidation-reduction mechanism. It is not yet established that the prothrombin molecule contains the chemical groups which characterize the vitamin K molecule. Perhaps the vitamin merely helps to maintain the prothrombin forming tissues in a productive state. “It has been suggested that vitamin K may insure the presence of the S-S group in the thrombin molecule, and Baumberger has proposed the hypothesis that thrombin oxidizes —SH groups of fibrinogen, thereby, converting fibrinogen into fibrin.”

Adequate amounts of fat soluble vitamin A are necessary for the normal integrity of the epithelium of the ocular, respiratory, gastrointestinal, and genitourinary tracts. Vitamin A is stored in the liver, and is rationed out from there to maintain normal blood plasma levels. This being so, the daily ingestion of sufficient amount of this vitamin does not of itself insure its proper utilization if the liver is diseased. Posner and Chinn found that rats fed on a low choline diet containing liberal supplements of carotene, developed livers poor in vitamin A. This fact seems to support the view that the vitamins and essential amino acids exert synergistic actions upon one another.

The rather recently discovered vitamin P is concerned with certain hemorrhagic manifestations. It, itself, is thought to be part of an oxidation-reduction enzyme.

**Early Toxemias of Pregnancy**

We feel that the early toxemias of pregnancy can also be correlated with our hypothesis, in that they are probably due to deficiencies in vitamin B (thiamin, pyridoxine, etc.), as well as methionine, choline, and cystine. The clinical manifestations may be explained by an accumulation of toxic metabolites as a result of incomplete carbohydrate, fat, and protein metabolism, as previously discussed.
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In addition, the liberation of choline and methionine from phospholipids and proteins by pancreatic enzymes is an essential step in the metabolism of these compounds. Recent experiments would indicate that hydrogen sulfide is necessary in the large intestine for the reactivation of pancreatic enzymes, so that they may be reabsorbed and taken to the liver. There, by selective absorption, they are returned to the pancreas as zymogens, to be reactivated into functioning enzymes. Hydrogen sulfide may be a by-product of intestinal putrefaction. Experimental data show that exocysteine peptides digested with rat liver extracts were degraded under controlled conditions to pyruvic acid, ammonia, and hydrogen sulfide. This mechanism may be the source of hydrogen sulfide for the reactivation of pancreatic enzymes. Here, again, we observe an interrelationship between choline, methionine, and cystine. It is possible that pancreatic enzymes, which should be transported to the colon, may be regurgitated by the patient with hyperemesis gravidarum due to the reverse peristalsis accompanying emesis. The extreme debility evidenced by these patients may not be due to dehydration alone, but also to an inability to absorb and assimilate essential foods. The morbidity will depend upon the depletion of the reserve stores of liver glycogen and fat, which can be metabolized as protein spacers.

Summary of Pertinent Physiologic Relations of Methionine, Choline, and Cystine

Methionine and cystine as sources of sulphydryl groups are important for maintaining
1. normal ergothionine content of erythrocytes,
2. normal glutathionine content of all cells for
   a. intracellular detoxifying processes,
   b. intracellular oxidation-reduction processes,
   c. normal synaptic function,
3. normal amount of taurocholic acid in bile.

necessary for
1. normal synthesis of insulin,
2. detoxifying indole and skatole in the liver,
3. normal carbohydrate, fat, and protein enzymatic activity.
4. neutralizing chorionic gonadotropin and pituitary antidiuretic hormone,
5. synthesis of fibrinogen by the liver.

probably essential for
1. synthesis of estrogens and progesterone.

Methionine and choline as sources of methyl groups, and as lipotrophic agents are important for
1. methylation of guanidoacetic acid,
2. neutralizing posterior pituitary pressor substance.
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4. neutralizing chorionic gonadotropin and pituitary antidiuretic hormone,
5. synthesis of fibrinogen by the liver.

probably essential for

synthesis of estrogens and progesterone.

Methionine and choline as sources of methyl groups, and as lipotropic agents are important for

1. methylation of guanidoacetic acid,
2. neutralizing posterior pituitary pressor substance.

---

**Table 1—Physiological Chemical Determinations**

<table>
<thead>
<tr>
<th>Blood Values</th>
<th>Normals</th>
<th>Pregnancy</th>
<th>Preeclampsia</th>
<th>Eclampsia</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coagulation time in minutes</td>
<td>1.5–2.5</td>
<td>less than 2.5</td>
<td>less than 1</td>
<td>In normal pregnancy albumin = 3 globulin = 1</td>
<td></td>
</tr>
<tr>
<td>Serum proteins in gm. %</td>
<td>3.6–5.4</td>
<td>2.9–4.3</td>
<td>3.6–0.95</td>
<td>In eclampsia albumin = 1.3 globulin = 1</td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td>1.5–3.4</td>
<td>2.3–3.8</td>
<td>0.36–0.95</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Globulin</td>
<td>0.18–0.35</td>
<td>0.3–0.7</td>
<td>0.36–0.95</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin in gm. %</td>
<td>10–13</td>
<td>14–21.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematocrit %</td>
<td>38.3</td>
<td>57</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythrocyte count</td>
<td>4,350,000</td>
<td>6,000,000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukocyte count</td>
<td>4,000–9,000</td>
<td>up to 35,000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets</td>
<td>300,000</td>
<td>350,000 to 600,000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood volume</td>
<td>23% increase</td>
<td>markedly decreased</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma volume</td>
<td>25% increase</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acid–Base pH</td>
<td>7.39</td>
<td>7.42</td>
<td>7.42</td>
<td>6.95–7.45</td>
<td></td>
</tr>
<tr>
<td>Amino acids in mg. %</td>
<td>5.8</td>
<td>6.5</td>
<td>6.5–22.1</td>
<td>12.1–22.7</td>
<td></td>
</tr>
<tr>
<td>Cholesterol in mg. %</td>
<td>80–250</td>
<td>270–331</td>
<td>320–379</td>
<td>320–379</td>
<td></td>
</tr>
<tr>
<td>Total Phenol &amp; Indoles %</td>
<td>1.83</td>
<td>same</td>
<td>may increase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N. P. N. in mg. %</td>
<td>25–40</td>
<td>22–30</td>
<td>31</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>B. U. N. in mg. %</td>
<td>5–23</td>
<td>6–13</td>
<td>10.5</td>
<td>15.6</td>
<td></td>
</tr>
<tr>
<td>Uric Acid in mg. %</td>
<td>2.5–5</td>
<td>same</td>
<td>4.6–6.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Increased in starvation, high fat diet, hemocoagulation, oliguria, or failure of formation and destruction of uric acid by the liver.
3. lipotropic activity in
   a. cholesterol and sterol metabolism,
   b. neutral fat and phospholipid metabolism,
4. synthesis of acetylcholine necessary for nerve impulse transmission,
5. synthesis of estrogen and progesterone.

Dietary Management

If the foregoing hypothesis and postulations are correct, the sources of methionine, choline, and cystine should be provided for in the diet of all pregnant individuals in order to prevent the establishment of the vicious cycle leading to toxemias of pregnancy.

General Considerations

From the standpoint of this study the relative intake of fat and protein is of prime importance. Certainly the elimination of all fatty meats, fried food, and foods containing shortening is in order, and the fat necessary for normal physiology should be derived from the more easily digested fat present in whole milk, eggs, and butter. The protein requirement for the pregnant woman must certainly be higher than that of the non-pregnant, possibly three times as high. However, we believe that there should be a predominance of food in the diet containing the essential amino acids, and choline, methionine, and cystine. Due to the fact that the choline-methionine-cystine ratio is of great importance, we feel that there should be a predominance of food in the diet containing the essential amino acids derived particularly from vegetables such as dried lima beans, peas, wheat gladin, and wheat germ. The value of dried brewer’s yeast should not be overlooked, for it contains 46.1 per cent protein, and 36.6 per cent carbohydrate, as well as being a very satisfactory source of vitamin B complex. It is proven wise when attempting to supply the thiamin need to couple it with other components of the vitamin B complex because of their synergistic action.

Prophylactic Diet

A suggested preventative dietary intake of these essential foods might be the daily ingestion of 1500 cc. of whole milk, coupled with 2 eggs (either well beaten raw in milk, coddled, or poached), and 1 daily serving of organ meat, or lean muscle meat. A daily intake of whole wheat cereals, and a complete protective vitamin consumption having its source from fresh fruits or vegetables (or derived artificially) must be furnished for the proper utilization of choline, methionine, cystine, etc.

Diet in Toxemias of Pregnancy

We can readily understand the efficacy of estrogenic substance, adrenal cortical hormone, and thyroid in the treatment of toxemias, but they are only substitution measures, and do not alter the primary metabolic causations of toxemia. Such measures will probably be of great value in the preeclamptic as adjunctive measures. It is a known fact that diabetic mothers fare better when estrogen and progesterone are added to the regime for their management. If the pancreas is unable to elaborate insulin, a sulphydryl compound, might it not also be unable to form other sulphydryl containing pancreatic factors such as pancreatic lipase? In order to effect change in the factors initiating the pathology of toxemias, there must be additional dietary restrictions, over and above those for the normal pregnancy. There should be further restriction of fat and muscle meat, with a complementary increase in carbohydrate intake to afford greater protection to the liver, and to discourage the retention of fats in this organ. The use of skim milk instead of whole milk should be resorted to in these cases.

Diet in Severe Preeclampsia and Eclampsia

In cases of severe preeclampsia and eclampsia the degree to which dietary regulations may prove effective is lessened, in as much as a vicious cycle is in progress leading to complete liver and kidney destruction. However, we believe that the use of intensive specific amino acid therapy, coupled with high carbohydrate administration, may, in the future, offer great assistance. The use of calcium and intensive specific vitamin therapy may prove to be valuable adjuncts. This we believe because irreparable damage to the liver and kidney, even in true eclampsia, is not as common as one would suspect.

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