Tufts Medical Journal

SIEGFRIED JOSEF THANNHAUSER, M.D., PH.D.

Professor of Clinical Medicine at Tufts Medical School; Associate Chief, Boston Dispensary and J. H. Pratt Diagnostic Hospital

S. J. Thannhauser.

Vol. VII, No. 2 Jan., 1941

BRIEF HISTORICAL NOTES ON MEAD'S CEREAL AND PABLUM

HAND in hand with pediatric progress, the introduction of Mead's Cereal in 1930 marked a new concept in the function of cereals in the child's dietary. For 150 years before that, since the days of "pap" and "panada," there had been no noteworthy improvement in the nutritive quality of cereals for infant feeding. Cereals were fed principally for their carbohydrate content.

The formula of Mead's Cereal was designed to supplement the baby's diet in minerals and vitamins, especially iron and B_1. How well it has succeeded in these functions may be seen from two examples:

(1) As little as one-sixth ounce of Mead's Cereal supplies over half of the iron and more than one-fifth of the vitamin B_1 minimum requirements of the 3-months-old bottle-fed baby. (2) One-half ounce of Mead's Cereal furnishes all of the iron and two-thirds of the vitamin B_1 minimum requirements of the 6-months-old breast-fed baby.

That the medical profession has recognized the importance of this contribution is indicated by the fact that cereal is now included in the baby's diet as early as the third or fourth month instead of at the sixth to twelfth month as was the custom only a decade or two ago.

In 1933 Mead Johnson & Company went a step further, improving the Mead's Cereal mixture by a special process of cooking, which rendered it easily tolerated by the infant and at the same time did away with the need for prolonged cereal cooking in the home. The result is Pablum, an original product which offers all of the nutritional qualities of Mead's Cereal, plus the convenience of thorough scientific cooking.

During the last ten years, these products have been used in a great deal of clinical investigation on various aspects of nutrition, which have been reported in the scientific literature.

Many physicians recognize the pioneer efforts on the part of Mead Johnson & Company by specifying Mead's Cereal and PABLUM.

Pablum is a palatable mixed cereal food, vitamin and mineral enriched, composed of wheatmeal (farina), oatmeal, cornmeal, wheat embryo, beef bone, brewers' yeast, alfalfa leaf, sodium chloride, and reduced iron.

Contents

Tufts Medical Journal

Published four times during the college year by the students of the Tufts College Medical School, Boston, Massachusetts in the interest of students, faculty and alumni. Printed at the Crimson Printing Company, Cambridge, Mass.

Manuscripts submitted to the Journal will be returned if requested. Reprints by special arrangement.

Subscriptions—$1 for the four issues.

Address all communications to the Tufts Medical Journal, 416 Huntington Ave., Boston, Mass.

Volume VII Number 2

Tufts Medical School Biographies

Dr. S. J. Thannhauser

Siegfried Josef Thannhauser, M.D., Ph.D. is Associate Chief of the Joseph H. Pratt Diagnostic Hospital and Boston Dispensary and Clinical Professor of Medicine at the Tufts College Medical School. His birthplace is Munich, in Bavaria where his ancestors on both sides have lived for centuries. One of them established the first postal service in Europe. A great uncle came to Boston after the liberal revolution of 1848 had been suppressed; several of his children are living,—"typical New Englanders." His father was a manufacturer as well as Commercial Councillor at the Bavarian Court. Always an idealist, he refused to make munitions in 1914, acting as Delegate to the Red Cross, while the government operated his plant. One of his uncles was a prospector in South Africa, where he was a friend of Cecil Rhodes, and made and lost a fortune before he died. When this uncle visited the family estate at Munich, young Thannhauser learned "to ride, to dress every day, and to speak English". These useful accomplishments were interludes of a childhood which was care-free and happy, with parents who had the means and inclination to be indulgent with their only child.

None of his relatives had been doctors, except for one paternal cousin, the noted August Wasserman. His father looked forward to a partner and eventual successor in the family business. However, the manufacturing of pewter ware, even of "Munich" beer steins, did not appeal. After completing a Humanistic course at the *Gymnasium* in preparation for business, Thannhauser decided to study art. His father accordingly sent him to Italy where he studied for some time. On his return to Munich, he entered the University to continue his artistic career. Here, the Professor was dull. The History of Dutch Art was a disappointment. Thannhauser left,—but not to join his father in business. He re-entered the University at once. This time he was a student of Medicine. His choice seems to have been based on an interest in pure science. After the first day of Anatomy, however, his future career was settled.

The program for a medical student in the German Universities is (or was) more flexible than our own curriculum. Students were encouraged to travel to different parts of Germany studying under leading men, wherever they might be located. Consequently, the next five years found him successively at Munich, Geneva, Kiel, and back again at Munich. At the latter place, he was inspired by the teaching and example of Friedrich von Mueller. He was already deeply interested in chemistry, his doctor's thesis being on "Formation of Homogentisinic Acid in Alkaptonuria". He graduated *summa cum laude*. During the preparation of this thesis, he felt that his training in Chemistry was inadequate. He, therefore, obtained from his father additional financial assistance to secure a doctorate in chemistry, after completing his medical degree. He studied in Adolf von Baeyer's laboratory. Baeyer has been called "The Father of Modern Chemistry". Here, Thannhauser wrote a thesis on "Constitution of Bilirubin and the Relation of Bilirubin Chemistry to Porphyrin Chemistry".

In order to qualify for his Ph.D. in chemistry, he had to take oral examinations in Physics and Chemistry. The examination in Physics was given by Wilhelm Roentgen, who had the reputation of failing 80 per cent of the candidates who faced him. There were two questions on the examination: First was a discussion of Poisseuille's Law. Poisseuille was a French *physician* who made some studies on velocity of flow in capillary tubes. This appealed to the famous *physicist* as an appropriate question to put to a doctor of medicine. The second question was: "Develop the physical basis of the apparatus of the inner ear." Roentgen had said to Dr. Thannhauser: "You are the first medical man that I have examined. Now you must suffer". He still remembers the examination, and describes it as "awful." The day before taking his oral examination in Chemistry, the young aspirant was expected to make an official call in full dress, with tail coat and white tie. Baeyer, synthesizer of indigo, and pioneer in pyrrol, pyridine, terpenes, nitrosos, and many other compounds was very affable. He discussed his favorite cathartic and even wrote a prescription for the candidate, wishing him well for the morrow. It was very amusing, but the next day he was no longer witty! The examination was no joke!

Having completed studies for degrees, and written theses in both medicine and chemistry, Dr. Thannhauser became assistant to Dr. Friedrich von Mueller who had influenced him greatly as a medical student and with whom he continued to work in the closest collaboration for fourteen years, interrupted only by four years of war. He started as Junior Resident, and by the time he left was Associate Director of the University Hospital, responsible only to Dr. Mueller.

His first medical publication, which appeared in 1913, concerned the well-known tolerance curves for sugar. This paper anticipated many later investigations on carbohydrate metabolism. It received scant attention at the time, or later. It remained unnoticed largely because of the choice of a weekly journal (Muenchener Medizinische Wochenschrift) as the medium for publication.

At the outbreak of war in 1914, Dr. Thannhauser volunteered immediately. He served in various capacities along the Western Front, beginning as an orderly, at the First Aid dressing station, and receiving successive promotions until he held the rank of Major and was placed in charge of a hospital of 300 beds for Kidney Diseases. This was a valuable experience and led to a monograph on War Nephritis. Meanwhile, he had found time to write a paper on the "Metabolism of Nucleic Acids and Gout" and had been promoted to a teaching position as *Privat-Dozent* at the University. Following the war, in addition to his teaching post, he was placed in charge of all the Medical Laboratories at the Hospital. He published a number of papers on the "Chemical Constitution of Nucleic Acid," on diabetes, on kidney disease, and on metabolic disorders.

About this time, he became interested in the lipids and their metabolism, but his chief, Friedrich von Mueller, objected to his doing research in this field. He expressed his opinions forcibly with the statement that lipoids were "dirty". Dr. Thannhauser quietly went ahead with his investigations, and wrote a paper on cholesterol metabolism without consulting his superior. Dr. Mueller did not like this and insisted that he confine his activities to gout.

In 1924, he was appointed Professor of Medicine at the University of Heidelberg. At a farewell dinner, Dr. Mueller told the new Chief he would surely succeed if he would only select an assistant such as he had been: "Ein Student der mehr weiss als der Chef, aber der nichts besser weiss" (A student who knows *more* than his chief, but who never "knows better.").

He received further appointments as Chief of the Medical Hospital at Dusseldorff, then the largest and most modern in Germany with 450 medical beds. Here Dr. Thannhauser completed his textbook on "General Metabolism and Metabolic Diseases" and was invited to build a new University Hospital of 300 beds at Freiburg. Three years after this was completed (in 1934), Dr. Thannhauser was forced to resign by the National Socialist Government.

He was permitted to continue his private practice (which had been the largest consultation practice in the country). The Rockefeller Foundation furnished a grant for a laboratory so that his research might continue. However, his situation remained precarious. Once before, after the inflation in 1922, when the future looked hopeless, he had refused to leave his home and his country to go to a hospital in Canada. "Only the rats would leave a sinking ship". Now, he declined an invitation to be Chief of Clinic at Istanbul. Finally, in 1935, an offer came from Dr. Pratt to join the medical staff at the Dispensary, and to accept an appointment at the Tufts College Medical School. As usual, when confronted with a problem, he consulted his wife.

Mrs. Thannhauser is a Bavarian by birth, a Catholic, a student of chemistry, and an excellent cook (Dr. Thannhauser is now on a rigid weight-reduction diet). She met her future husband while he was still a medical student; he

proposed to her within an hour. The young couple then waited nine years to get married since Dr. Thannhauser was earning the equivalent of twenty-five dollars a month, and they wished to be independent to parental assistance. In 1917, they married while he was home on leave. Starting out very simply, they had by this time received every honor in the medical world. Their house was one of the "show places" of Freiburg. Naturally, they did not wish to leave but Mrs. Thannhauser was seriously concerned for the safety of her German-born Jewish husband. She knew of his admiration for the Reverend Martin Niemöller, then in a concentration camp. She had heard him say that the strength of the National Socialist Movement was the willingness of its followers to suffer, to die if need be, for their "religion". She knew his feeling that the opponents of National Socialism have to prove the same willingness to die for their ideals and for liberty. When the invitation arrived from Boston, she quietly crossed the border, and without notifying her husband, cabled his acceptance. She returned to confront him with a "fait accompli". It was the one important decision of their married lives which had not been decided in complete collaboration. She has been completely happy in the United States; her three daughters are attending college, and are "150 per cent American".

In his spare time, Dr. Thannhauser is an enthusiastic golfer, going around in 95 when he is "good" and 105 when he is "bad". He would rather play tennis, and prefers singles to doubles. He still enjoys skiing, at which he excelled when he was younger. He also played soccer with the Munich Sports Club (there being no University teams), was on the tennis team, and ran the 100-meter dash. He has retained his early interest in art as a hobby, and has made a fine collection of carved Gothics and wood plastics.

While still retaining an interest in pure science "as a hobby", in his serious work he has steadfastly followed the clinical approach. This approach to scientific research he believes to be inexhaustible. The patient and the bedside furnish the only sure road to an understanding of medicine.

Dr. Thannhauser enjoys talking about his coworkers and teachers, is almost diffident about himself. He feels that the more recent arrivals in the United States are greatly privileged to be able to work and to make some contribution in the country of their adoption, that those who have a longer residence here can more appropriately take the center of the stage.

In Europe he was admitted to membership in the Academy at Madrid, the Medical Association in Sofia, and the Italian Academy at Milano, not to mention the many decorations from his own country and government. He has just published a book entitled "Lipidoses: Diseases of the Cellular Lipid Metabolism". When asked about this, he said, "Have you seen the dedication"? His eye lit up, as he pointed to the title page. The lines read:

"In deep devotion to the Land of Freedom which has ever been a shelter for the victims of Intolerance."

H. Barry, Jr.

Clinical Pathological Conference

Case No. 6

presented by Robert W. Riemer, A.B.

T.R.M. (#4065-A-40-15 Cambridge), a 22 year old Scottish boy was admitted to the hospital in January 1940, complaining of headache, nausea and vomiting.

Six years ago this patient was troubled with "sore throats and small lumps" in the neck. He entered a large medical clinic at that time for a complete medical examination. Briefly, the following facts were elicited: red blood cells and white blood cells and 5% albumin were found in the urine; the urine showed a mixed culture, comprising staphylococci, diphtheroids and nonhemolytic streptococci. These organisms were obtained on culture from the urine from both kidneys. The blood pressure at that time was 110/90 and the NPN was 33. The boy had his tonsils and adenoids removed and in the course of time was discharged from the hospital. One year later he returned to the clinic for an annual clinical examination and the following significant findings have been recorded: urinalysis showed 0.3% albumin; staphylococci and nonhemolytic streptococci were again recovered from both kidneys; the blood pressure at this time was 125/90. About 1 year later the patient again reported to the clinic for a second follow-up examination. This time red and white blood cells were recovered from the urine. The latter contained one percent albumin. A PSP test revealed 10% in the first 15 minutes and a total of 35% in one-half hour. The blood pressure had not changed since the last examination. At this time we are told that the occular fundi were negative. Diagnoses were, of course, made by the clinic at the time of each clinical study. For the next four years the patient experienced little difficulty except for slight nocturia. These years he spent at college and kept well up in his work. At about the end of this period, he began to notice slight dyspnea on physical exertion and this was accompanied by thirst and polyuria. These symptoms gradually increased and gradually were complicated by a rather troublesome cough and orthopnea. The patient was digitalized at this time.

About one month before his admission to the hospital in January, while attending college, he began to have moderately severe headaches, almost daily, which were accompanied by unusual fatigue and drowsiness. These headaches, however, could be relieved medically, and he was able to continue at college with his studies. Gradually, however, his vision began to fade, first in one eye then in the other. This progressed to the point of almost complete blindness. Just before his admission to the hospital, his headaches became more persistent. They were severe and seemed to be localized over the frontal areas. And now, for the first time, he experienced nausea and vomiting.

On admission to the hospital, he is described as being a well developed, but poorly nourished young man showing extreme pallor. He was unable to respond clearly to questions and his breath had a strong uriniferous odor. The eye grounds showed striking narrowing and tortuosity of the arteries with flame-shaped hemorrhages, white patches of exudate and papilloedema. The heart was enlarged and revealed a gallop rhythm. P_2 was greater than A_2. The blood pressure was 200/160. There was no pitting edema in the extremities. The temperature was 99.5, the pulse 90 and the respirations 20. The urinalysis was of particular interest: sp. gr. 1.008; albumin 3 plus; white blood cells 0-2; and red blood cells 2-8 per high power field. The blood count was 3.4 million red blood cells and 8,000 white blood cells, with 74% PMN. Hgb 63%. NPN of blood was 100 mg%. The chlorides were 544 mg.% and the CO_2 combining power was 45 vol.%. The blood Hinton was negative.

With rest and fluids the patient improved somewhat subjectively. Repeated urine examinations showed a maximum concentration of 1.009 with a continually heavy trace of albumin. The blood NPN fell slightly to 90 mg.%. The serum

protein was reduced to 4.6 gms.%. A PSP test done during this admission revealed a total excretion of 25% in one hour with only 10% being excreted in the first 15 minutes. X-rays of the chest confirmed the clinical diagnosis of cardiac hypertrophy and in addition showed some tortuosity and elongation of the aorta. The patient remained in the hospital about one week in all and, after these various tests, was discharged as being unimproved.

Now a period of five months elapses, during which time the patient returned to college and was able, with some difficulty, to continue with his studies. His vision from time to time had improved somewhat, but we are told that, because of this, he frequently needed aid in walking from place to place. During the latter two months of this interval he experienced a gradual and progressive increase in dyspnea, and headaches were experienced almost daily. At times nausea was severe, and his appetite was very poor. His attending physician obtained blood pressure readings as high as 240/160. His nocturia had persisted and had become more noticeable. About a week before his final admission, he had noticed that, in voiding, his urine was pale red; and during this latter period, he had been unable to sleep unless propped up with pillows. Edema of the ankles had now made its appearance. Because of increased orthopnea, he was again re-hospitalized.

At the time of his last admission, his pallor had increased and cyanosis of his lips and nail beds was quite striking. He sat up in bed in obvious respiratory distress. Examination of his chest showed diminished breath sounds with slight dulness and coarse bubbling rales in both lower lung fields. Pitting edema in the extremities had now become quite marked. The heart was more dilated and the sounds remained regular, though rapid. The blood pressure taken shortly before he died was 190/170. The temperature was 99, the pulse 110 and the respirations were 35. The urine findings were the same as on previous examination. The blood NPN rose to 115 mg.%. The total protein remained about the same, namely 5 gms.%. The vital capacity was reduced to 1200 cc. An EKG showed abnormal T waves (the patient had been on digitalis for about one year) and there was also left axis deviation. The NPN rose to 170 mg.%. As treatment, he was given clysis and intravenous therapy, but failed to show any improvement. On the third hospital day, his condition suddenly turned for the worse, and he expired after several hours in an oxygen tent.

Differential Diagnosis

Dr. H. Baker:* We have a patient who at the age of 16 was troubled with "sore throats and small lumps in the neck"—probably glands. At this time he had a medical check-up, the positive findings being red cells and white cells and 5% albumin in his urine along with a culture of mixed organisms. Blood pressure and NPN were normal. One interesting fact we would like to know is the time relationship between his sore throat and the onset of urinary findings. We do know clinically that in this age group acute glomerular nephritis may follow a streptococcus infection, such as a sore throat, after an interval of about 10 days. Thus we could tie up this patient's sore throat with his urinary findings. Furthermore, with the onset of acute glomerular nephritis patients may have symptoms ranging from extremely mild ones to those of uremia. The mild symptoms can easily go unnoticed, and only the examination of the urine would give the clue as to the diagnosis. This may account for the lack of any history of symptoms with the onset of this case. Then again one may recover completely, i.e. symptomatically and from the laboratory point of view, so that without a past history it would be impossible to know that the patient did have a renal involvement in the past. Of course others may have varying gradation of symptoms and signs making the diagnosis fairly simple. These again may heal, may become subacute, or enter a chronic stage—usually accompanied by phases of acute exacerbations of signs or symptoms or both, over a period of time.

This boy had a T&A, after the damage to the kidneys had been done, in the hope of preventing further damage in the future. One year later his annual examination showed only a small amount of albumin and some organisms

*Asst. Professor of Medicine, Tufts Medical School; Visiting Physician, Boston City Hospital.

but no other signs or symptoms of activity. Again the next year an examination showed red cells and white cells and some albumin, probably a flare up or possibly a subacute form. However the fundi, blood pressure, etc. were normal. These negative findings pointing against a chronic phase since one would expect increased blood pressure, fundi changes, low fixed specific gravity, nocturia, etc. in a chronic nephritis. The patient then goes along fairly well for almost four years except for beginning nocturia. However he may have progressed to a chronic latent stage—for in this stage there may be no symptoms at all or only minor ones. However this could be ascertained by looking for evidence of peripheral vascular disease such as hypertension, retinitis, cardiac enlargement, etc. plus the urine examination with some possible help from the renal function tests. None of these facts are mentioned in the history but we are now told that a rapidly progressing chain of symptoms are taking place, therefore I wonder as to the probably existence of some prior evidence of any peripheral vascular disease. The beginning nocturia and later polyuria and some thirst may be evidence of the need of more water to get rid of waste products and the loss of power to concentrate urine—signs of the chronic process. We now hear of slight dyspnoea gradually increasing, the cough and orthopnea, the patient being digitalized. In other words we are dealing with a cardio-vascular renal condition. About one month before admission to the hospital in January, 1940, severe headaches appear with unusual fatigue, probably on a hypertensive encephalopathy basis. Drowsiness, gradual loss of vision, and finally nausea and vomiting—uremic symptoms.

Admission physical examination showed a poorly nourished young man and extreme pallor consistent with progressing chronic nephritis. He was unable to respond clearly and his breath had a strong uriniferous odor—i.e. consistent with uremia. Eye-grounds showed marked pathological changes consistent with chronic arterial changes and the hemorrhages (fresh), exudate and papilloedema of uremia—probably malignant phase. The heart as we would expect was enlarged due to the hypertension and the presence of gallop rhythm indicates muscle damage. The blood pressure is given as 200/160—a very high diastolic pressure. Urine of low specific gravity, the somewhat lowered red count (toxic depression plus frequently deficient diet), NPN of 100, lowered chlorides, and slightly lowered CO_2 combining power (usually lower)—these findings are consistent with uremia.

With the rest for the heart and blood pressure and fluids to combat the nitrogen retention and help elimination, the patient felt better. However repeated urine concentrations showed a maximum of 1.009, therefore low and fixed. The heavy trace of albumin with lowered serum protein of 4.6 suggests a nephrotic syndrome in which dietary deficiency may be playing a part. The NPN is still elevated and the PSP test somewhat lowered. X-rays confirm the enlargement of heart and also show arterial changes as in the aorta.

Despite the fact that he was discharged unimproved it is remarkable that he could return to college with all his symptoms. Of course one might doubt the wisdom of this course. Soon however his symptoms progressed—dyspnoea, nausea, headaches, etc. His blood pressure was 240/160; urine pale red, question of blood; and thus the patient presents signs and symptoms consistent with the malignant phase of hypertension. Marked orthopnea and ankle oedema are now present. The last admission showed much cyanosis, marked pitting oedema of extremities, respiratory distress with diminished breath sounds and rales at lung bases, heart more dilated; in other words congestive heart failure. Blood pressure 190/170, very high diastolic with small pulse pressure and rapidly increasing NPN. Patient failed to respond and died on 3rd hospital day. No mention is made of a pericardial friction rub which is frequently present in terminal uremia, therefore this diagnosis cannot be made clinically. In view of the cyanosis and some temperature with respiratory distress one also has to bear in mind the possibility of pulmonary infarction, however cardiac failure could explain the cyanosis.

Diagnoses:

Chronic Glomerular Nephritis with Uremia, Malignant Phase.

? Chronic Pyelonephritis.

Hypertensive Heart with Congestive Failure.

Arteriosclerotic Changes as seen—eye-grounds and tortuous aorta.

? Terminal Hypostatic Pneumonia.

In going back over the case what other possibilities are there? First the kidney—since the urine was the initial and only positive finding. It is surprising that no mention is made of casts at any time. However, I feel that they must have been present, at times, at least. Red cells, white cells, and albumin which were constantly reported may exist in many conditions in the G.U. tract such as calculi, tbc., tumor, polycystic kidneys, pyelonephritis, etc. At no time was there any history of pain, bladder symptoms, hematuria (except microscopic) or X-ray findings pointing toward stone. Repeated urine cultures did not show tubercle bacilli (no guinea pig inoculations reported), and there was no tbc. history, nor G.U. X-ray findings, etc. suggesting tbc. Also one does not get the hypertensive phase with tb. kidneys. The course of events indicated bilateral involvement, and with no physical or X-ray findings of tumor—the diagnosis of growth seems unlikely. One might speculate as to polycystic kidneys, but no masses were reported, and as no other evidence such as pain, and at times gross hematuria, etc. was present which might lead to this diagnosis, I cannot rule it in. Also renal failure in polycystic kidneys usually occurs between the ages of 40 and 60, and this boy was only 22. The presence of pyelonephritis is more difficult to exclude. Usually one may get a history of "pyelitis" with chills, temperature, pus in urine, pain and tenderness especially costovertebral. All we have in this case is a 99° temperature and occasional white cells on the Jan. 1940 admission. However, at other times white cells (amount not given), and red cells were reported but none of the other characteristic findings. Nevertheless, a smoldering low-grade infection cannot be excluded entirely. The repeated presence of many red cells would probably favor glomerular rather than pyelonephritis. In the later stages of pyelonephritis with severe hypertension showers of red cells due to rupture of small blood vessels may be present from time to time, but in this patient the red cells were present during the first few years with a normal blood pressure. Once the severe hypertension develops in chronic pyelonephritis headache, eye-ground changes, high diastolic pressure, uremia, heart failure, etc. may develop—in other words a picture similar to that of this patient's. Therefore a past history of renal infection is so important for a clinical diagnosis. One must not forget that the clinical features of the end stages of nephrosclerosis, chronic glomerulo-nephritis, or chronic pyelonephritis may be so similar that without the past history of active renal infection, a clinical diagnosis of chronic pyelonephritis may not be possible. Therefore, the diagnosis of chronic pyelonephritis cannot be completely discarded. The history of the case and its course point more toward progressive glomerular nephritis.

Next we have the definite changes in blood pressure. The first examination 6 years ago showed a pressure of 110/90, one year later 125/90, again 2 years later still unchanged, but at the end of 6 years a marked hypertension. In other words, a normal blood pressure for at least two or more years in the presence of urinary findings rules out hypertension as the precipitating factor, making the hypertension rather a late result secondary to the kidney condition. Next we have heart failure playing an important role in the downward progress and death of the patient. Congenital heart can be easily ruled out on the absence of any history or physical findings. Rheumatic heart—no history except "sore throats", but no findings such as endocarditis, etc. X-ray did not show any rheumatic deformity. Cariac hypertrophy can be explained on the marked hypertension and the accompanying sclerotic changes. These latter findings along with toxic effects of the nephritis can explain the cardiac failure.

I believe this patient had an acute glomerular nephritis which progressed to a chronic glomerulo-nephritis with marked hypertension and sclerotic changes, cariac hypertrophy and congestive failure and the accompanying uremia—malignant phase. I cannot rule out the possibility of the patient's having had an acute pyelonephritis at the onset of his disease, but I believe the chronic glomerulo-nephritis in its malignant phase was the cause of his death.

Pathological Discussion

Before discussing from the standpoint of pathology the sequence of events in the course and ultimate outcome of the disease, and before attempting to correlate and interpret the findings, we first must know what the findings were. Now, here are the findings: chronic glomerulo-nephritis, healed bilateral pyelitis, chronic cystitis; cardiovascular hypertrophy, dilatation of both left and right ventricles, diffuse and severe arteriosclerosis of both coronary arteries, moderate arteriosclerosis of both the aorta and renal arteries, advanced arteriosclerosis of vessels of spleen, meninges, kidneys and eyes; plethora, hydraemia and anaemia, diminished coagulability and prolonged clotting time; *Signs of circulatory failure*: bilateral pulmonary edema, bilateral hydrothorax, ascites, pitting edema of both lower extremities, moderate congestion of systemic and portal venous systems, congestion, edema and hydropic degeneration of liver; edema of spleen, pancreas, meninges, brain and retina; dilatation of lymphatics with edema of lymph nodes, edema of scrotum and tests. *Signs of Uremia*: serofibrinous pericarditis, terminal gastro-entero-colitis with capillary bleeding into the mucosa, hyperplasia of parathyroids, atrophy of testes, regressive changes in nerve cells of both cortex and basal ganglia, regressive changes in ganglion cell layer of retina, edema of optic nerves with protrusion of nerves into posterior chamber of eyes; hypoplastic degeneration of bone marrow. Regressive changes with atrophy of the chromophil cells of the adenohypophysis. Lipoid storage in cortex of adrenal. Anomalous development of right lung. Single accessory spleen.

In considering the sequence of changes during the course of the disease, I believe it possible to begin with the kidney and trace directly or indirectly most, if not all, of the remaining changes to pathology of the urinary system. That is to say, the most significant single lesion is to be found in the kidneys. Other findings play an important but subordinate role.

Just a word about the kidneys grossly. They were loosely embedded in edematous fibro-fatty tissue that was firmly adherent to the true fibrous capsule. The latter was gray, opaque, thickened in areas, firmly attached to the cortex of the kidney, and was almost inseparably attached in the region of the pelvis. The kidneys resembled one another. Their contour was maintained, but they were uniformly reduced in size and weighed only 100 grams each. The renal arteries had thick walls and presented gaping lumina. There was no stenosis of either renal artery at its origin from the aorta. The renal veins were large and dilated. The kidneys were firm and were somewhat mottled yellowish gray to reddish brown. The superficial surfaces were uniformly and finely granular, the granulations varying from 1-2 mm. in diameter. There were no coarse scars and there were no fresh hemorrhages. The kidneys cut with resistance. The cortices were reduced measuring only 0.4 cm. in width. The finer markings did not stand out clearly and the pattern of cortex, medulla and medullary rays was obscure. The pyramids were reduced in size. The calyces and pelvis were slightly dilated. The walls were thick, gray, opaque, quite smooth and free of hemorrhage. Lymph nodes at the hilus of each kidney were moderately enlarged, gray and moist. The ureters, the bladder and the urethra were carefully examined and there was no sign of obstruction.

On microscopic examination, it is at once apparent that there are two distinct and, I believe, independent lesions in each kidney. One of these is an old healed pyelitis which dates back to the beginning of the illness. The other is more recent and is characterized by a chronic, diffuse, inflammatory reaction that has involved all glomeruli. Primarily it is the glomeruli that are involved, but, and this is well recognized, any long-standing inflammatory reaction involving one part of an organ as complex as the kidney, for example the glomeruli, sooner or later leads to changes in the tubules, stroma and vessels as well. In other words, the entire kidney is now in a pathological sense involved.

In respect to the ultimate outcome, I believe that this patient died as the result of asphyxia, subsequent to the increasing bilateral pulmonary edema and hydrothorax. These changes, in turn, may be traced back to a failing myocardium with extreme hypertension and with severe coronary sclerosis. The hydraemia, plethora, anaemia, an-

(*Continued on page* 60)

Benjamin Rush

by John J. Whoriskey, Jr., A.B.

The period of the American Revolution has given to us a host of colorful personages who have become great names in our history and heroes in our legends. One of the most colorful of all this company was Benjamin Rush, who not only found time to serve his country with conspicuous ability, but also managed to win for himself a distinguished position in American Medicine as a great physician, as a scientist, and as one of the founders of medical education in this country.

Benjamin Rush was born on the 24th of December 1745 on his father's plantation in Byberry near Philadelphia, the sixth child of John Rush, blacksmith and gunsmith, and Susanna Harvey Rush, a brilliant, accomplished, and unusually well educated woman. When Benjamin was only six years old his father died, and his family was forced to move to some property he had owned in Philadelphia in order to make a living. Mrs. Rush opened a store which enjoyed success, apparently from the very first. Benjamin and his younger brother Jacob were sent off to the school of the Reverend Doctor Samuel Finley, their uncle in Nottingham, Maryland.

Dr. Finley, afterwards President of Princeton College, was a stern but just school master, eminently qualified for the education of the minds and character of boys. Unquestionably the nine years which he spent in this school were of paramount importance in forming the character of young Benjamin Rush. It was here that he learned to fight with perserverence and ferocity for what he believed to be right and with a narrow singleness of purpose which was to make his adult life one long controversy as he tried to force a stubborn and protesting world into what he sincerely felt to be proper channels of thought.

At the age of fifteen Benjamin was accepted into the College of New Jersey at Princeton where he received his degree in one year. He was now ready to determine what should be his career. Fully aware of his undoubtedly unusual gift of oratory and urged by enthusiastic friends, Benjamin decided to study law. When he informed his uncle, Dr. Finley, of his decision that worthy and pious gentleman threw up his hands in horror. The law would never do. It was full of temptations! He advised Benjamin to enter the study of medicine where either the opportunities or remuneration for dishonesty were presumably negligible. Accordingly, Benjamin entered his apprenticeship with Dr. John Redmond of Philadelphia and applied himself to his work with such diligence that he informs us he was absent from his master's shop only eleven days and three evenings in the next five years. His duties were largely those of a nurse and apothecary, and Benjamin made use of every moment of his spare time to follow Dr. Redmond about the wards of the Pennsylvania hospital and to read all the medical texts available to him. He supplemented his education by attending the lectures of Shippen and Morgan at the newly founded Medical School of the College of Philadelphia.

In the last year of his apprenticeship Rush developed an interest in politics through his opinions upon the subject of the famous Stamp Act and following its repeal his political views were never free of a deep rooted antipathy for the Crown.

In August, 1766, Benjamin set out for Edinburgh and spent two years of study at the University, receiving his medical degree after demonstrating the acidity of the contents of his own stomach by a series of experiments which must have been highly unpleasant to him, involving as it did mainly the regurgitation of various foods at varying intervals after their ingestion.

Dr. Benjamin Rush returned to Philadelphia secure in the conviction that he knew as much, if not more medicine than any of his colleagues. Lacking the necessary, or at least desirable, political, social, and religious connections to launch him into practice with instant success, Dr. Rush sought to enhance his reputation by securing an appointment to the faculty of the Medical School of the College of Philadelphia as Professor of Chemistry. The value of such prestige in gaining the patronage of wealthy patients and

the cooperation of his fellow physicians Dr. Rush completely nullified by setting both these important groups of people into a hostile frame of mind. The physicians he estranged by solemnly informing them that Boerhaave's system of medicine, then in vogue in America, was entirely fallacious in its concept of the location of disease in the fluids of the body when Benjamin Rush knew all the time that Cullen's system, based on the location of disease in the solids, was the only correct one! At first the entire medical profession in Philadelphia was arrayed against Rush and he complained that for the first seven years of his practice he had not a single patient referred to him from his colleagues. Many years later when all the Philadelphia physicians had swung over to the Cullen school of thought, Dr. Rush started the whole controversy over again by denouncing Cullen and battling vigorously for his own system of medicine..

He estranged practically all the wealthy and influential families of the city by his vigorous attacks on slavery. Under the circumstances, Dr. Rush was forced to draw his clientele from among the poor of the city, and this he did, feeling fully compensated for a dearth of fees by the spiritual gains which he felt the work brought him and by the unlimited opportunities for observing diseases and trying out medicines. He also began to spread his reputation by a series of popular writings, addressed to the general public, upon the need and benefits of regular exercise and a regulated life.

In 1773 when Dr. Rush was 27 years old he fell in love with Sarah Eve, the beautiful and gracious daughter of a sea-captain. They planned to marry in December of 1774 but three weeks before the wedding date Sarah died of a lingering disease which Benjamin Rush found himself powerless to combat. Although he was overwhelmed with grief by his great loss, strangely Dr. Rush completely ignored this episode in his life when he wrote his precise *Memoirs* in 1800. Before many months he formed a new attachment for Julia Stockton, the lovely sixteen year old daughter of one of his oldest friends. He made several journeys to Princeton to conduct a rather formal courtship and in January of 1775 the happy couple were married. It is an interesting commentary upon the general state of health at the time that sixteen children resulted from this marriage, of which nine survived—this in a physician's family.

It was at about this time that Dr. Rush was becoming more and more interested in the political problems of the day which were so soon to flare up into a war with the Crown. He had collected material for a propaganda pamphlet against taxation without representation and supporting American independence. Fearful of the effect of publication of his seditious document upon his practice in the Tory city of Philadelphia, Dr. Rush was in a quandary as to a method of enjoying a controversy without being identified with it. The solution of his problem appeared in the person of a young Englishman, Thomas Paine, for whom he conceived a great respect upon short acquaintance. Dr. Rush invited Paine to utilize the material and write the pamphlet. Paine agreed and wrote the document, often coming to Dr. Rush for criticism and advice. When the pamphlet was completed, Benjamin Rush chose a title for it, and Thomas Paine's *Common Sense* was published. The ultimate effect of this extraordinary document was the American Revolution.

The Continental Congress which had met in Philadelphia dissolved in a quarrel over a resolution of independence and on June 18, 1775 the Conference, appointed by a mass meeting of citizens and including Dr. Rush in its membership, met to call another general convention. On June 23, Benjamin Rush offered a motion to draft an address in favor of American independence and was delegated to prepare such a report. This he delivered the next day and it was adopted with enthusiasm. This report was submitted to the new Congress, and many of its salient points and much of its phraseology were included in the Declaration of Independence, issued on July 4, 1776. Dr. Rush was elected to Congress, and in August became one of the signers of this declaration.

Congress was, of course, an ideal battle ground upon which any of a number of controversial points might be raised and Dr. Rush soon found a sore point upon which he arrayed

the rest of that august body against himself. In short, he objected to the system of government, especially the unicameral legislature. Although his recommendation of a government based upon a bill of rights, a constitution, and laws was later to be accepted as the theory of government in the United States, at the time the aggressive Doctor merely achieved the loss of his seat in Congress.

In April 1777, Dr. Rush accepted a commission in the Medical Department of the army, and plunged directly into a fight which proved a source of embarrassment to a large company of distinguished personages, including himself. In 1775 Dr. John Morgan, one of the founders of the Medical School of the College of Philadelphia, had been appointed Director General of the Medical Department of the army. Congress split the authority between Morgan and William Shippen, Jr., and then dismissed Morgan, who spent two years seeking the hearing that was to vindicate him completely, after his heart had been broken. Dr. Rush was outraged at the conditions which he found in military hospitals. Discipline was unknown and ambulatory patients were unmanageable, disrupting hospital routine and efficiency by their brawling and mischief making. All Dr. Rush's pleas for a military police were unheeded. With a rapidly mounting rage he watched the results of mismanagement and graft for which he blamed his superior and finally launched an attack on Shippen with a bitterness and energy which could not be ignored. A reluctant Congress opened an investigation of Dr. Rush's charges and, under strong influence, exonerated Shippen and ordered Rush to resign. This he did, and commenced preparations, in his disgust, to take up the profession of law when the evacuation of Philadelphia by the British encouraged him to return home. Morgan received his hearing at this time and following his vindication made formal charges of malpractice and treason against Shippen in the military court, thus forcing the entire controversy upon the unwilling hands of a court martial. Joyously, Dr. Rush rushed back into the fray, and, although the court martial acquitted Shippen, Congress dismissed him, only to reappoint him under strong political pressure. Once again Dr. Rush furiously attacked Shippen's mismanagement of the Medical Department and finally, in 1781, forced his resignation.

The part played by Benjamin Rush in the American Revolution cannot be passed over without some comment upon his quarrel with General Washington. Until well after the Battle of Saratoga, the brilliant victory of Gates and Arnold, Washington's abilities were unknown to his colleagues. The great leader of the future had not yet shown himself, and the inactivity of the Commander-in-chief contrasted strikingly with the signal success won by his subordinates. Gates and Conway, jealous of Washington's authority, were working for his downfall, forming the little known conspiracy sometimes referred to as the Conway Cabal. Washington was aware of their plotting. Dr. Rush was not. To him it seemed that the Commander-in-chief was discriminating against the deserving Conway and he began to address himself to various men in authority, protesting such partiality. Once he had the argument under way, Dr. Rush began to appreciate grave faults in the management of the American Army and he communicated his criticisms in an unsigned letter to Patrick Henry. The motives which prompted the failure to sign this letter are unknown. Henry immediately recognized the author and dispatched the incriminating document to Washington who, in his bitterness, passed some remarks implicating Benjamin Rush in the Conway Cabal, when actually the bombastic Doctor was unaware of its existence, and working only for the best interests of his country. It is interesting to observe that Dr. Rush never denied the authorship of the letter, even when Washington's biographers were to publish it in such a manner as to reflect unfavorably upon the motives which prompted its composition.

Following the war, Dr. Rush returned to the re-chartered Medical School, now of the University of Pennsylvania, only to find that Shippen had already joined the staff. It took him all of a year to swallow his rage, and renew his teaching duties as a Professor of Chemistry. In 1789 he was appointed to the chair of theory and practice of Medicine. He taught his students to observe nature by learning diseases first at the bedside, and secondly from reference to books.

In August, 1792, Philadelphia was struck by a terrifying epidemic of yellow fever. None of the early cases excited apprehension, the physicians believing them to be uncommonly malignant cases of "bilious fevers." Dr. Rush compared notes with his colleagues and soon became convinced that Philadelphia faced a dangerous epidemic of an extremely serious disease. He believed that the epidemic took its origin in the miasmata arising from a load of spoiled coffee putrefying on the wharves and always contended that he traced the earliest cases directly to this source. Once the disease had gained a foothold he believed it was spread by contagion although he was to repudiate his convictions on this matter in later years.

In his urgent efforts to prevent the spread of the dread epidemic, Dr. Rush succeeded in initiating one of the bitterest of the controversies which form a large part of his life story. As before, he stood practically alone and succeeded in antagonizing several groups of people. His publication of the supposed domestic origin of the yellow fever arrayed practically all who had business interests in Philadelphia against him, these groups vigorously contending that the disease had been carried in on foreign ships and citing their evidence in proof. Dr. Rush antagonized the medical men by his treatment, regarded by them as radical and of doubtful value. In the course of an argument of increasing bitterness many of these men, it is to be hoped through ignorance, banded together to deny the existence of yellow fever in Philadelphia and to denounce Dr. Rush for spreading false reports to enrich his practice. His temper fully aroused, the volatile Doctor fought his adversaries by every means at his hand and it is largely to this quarrel that we owe the existence of several excellent descriptions of this, and succeeding epidemics of yellow fever in Philadelphia published by Benjamin Rush.

It was upon the matter of treatment that the struggle centered. The disease rapidly reached epidemic proportions and thousands fled the city in terror. No longer could the existence of the fever be denied. Dr. Rush purged his patients vigorously and bled them enthusiastically. It was upon the latter point that he excited the vitriolic attacks of Cobbet, a libelous editorial writer with a low reputation. Dr. Rush bled his patients copiously in amounts often well in excess of a hundred ounces! Cobbet declared editorially that more patients died of exsanguination than succumbed to the fever. Unable to keep within the bounds of decent expression, this cheap hack writer exposed himself from the first to charges of libel which Dr. Rush soon brought against him. Cobbet was ruined by the damages, which Dr. Rush paid to charity, and he moved to New York to declaim against his enemy and the court which had fought against him. In this and succeeding but milder epidemics of the yellow fever Dr. Rush continued to quarrel with his associates, but never with the bitterness which marked the original controversy.

Dr. Rush had always had a particular interest in insane patients and succeeded, by sheer persistence of argument, in so far wearing down the resistance of the trustees of the Pennsylvania Hospital as to secure the building of a new wing for the care of the insane in healthful and comfortable surroundings. He instituted treatment with baths, from which our modern hydrotherapy has grown. Occupational therapy as we know it today was another of his innovations. Some of Dr. Rush's ideas for the restraint or calming of violent patients, on the other hand, had to be dropped. An example of such treatment was a large turntable upon which the patient was spun to stimulate the flow of blood to the brain by centrifugal force. Since the device merely served to excite the patients, if it did not injure them physically, the practice was soon dropped. But the fact must not be lost sight of that Rush was one of the very first modern psychiatrists. He gave great impetus to this newly founded branch of scientific medicine by the publication, in 1812, of a text book which was to stand as the authority in the field of mental diseases for the next seventy years. In this, his greatest work, he clearly set forth most of the mental diseases as we know them today although he described their etiology, in a series of sweeping statements, to

(*Continued on page* 60)

Studies In Uncommon Diseases

No. 2: Weil's Disease or Spirochetal Jaundice

by C. J. Antonellis, A.B.

In the interests of accuracy the above title should be qualified by the statement that the disease may possibly not be as uncommon as has been thought and that in addition it need not show any jaundice. In fact, only 50% of the proved cases ever show jaundice (1). Thus, if the occurrence of jaundice is made a diagnostic criterion the actual incidence of the disease will be incorrectly measured. In their review of the disease Jeghers and Houghton suggest this as a possibility; their paper reports the first case of proven Weil's disease in the United States and appeared only five years ago in 1935 (2).

However, it was in 1888 that Weil first described as an entity the combination of jaundice, enlarged spleen and liver, and nephritis that bears his name (3). And it was fully a quarter of a century later that Inada, the Japanese investigator, recovered a spirochete from a patient with the disease; two years later Noguchi was able to cultivate the organism and to show that the spirochete was found outside the red blood cell. He also demonstrated that the blood of an infected patient caused reactions in the guinea pig only if collected in the first week of the disease.

In its clinical course the condition is generally divided into three stages, and since most texts do not consider it very fully we shall attempt to present a fairly complete account of a typical case. The first or febrile stage is ushered in abruptly with the usual picture of acute infectious disease. There is great prostration, chills and high fever, headache, pain behind the eyes, often conjunctivitis, and a more or less typical myalgia which most often is referred to the muscles of the calves. Such a localization should always suggest at least a fleeting consideration of Weil's disease. Gastro-intestinal symptoms such as diarrhea often occur, herpes labialis is common, and there may be a skin eruption resembling the exanthem of scarlet fever (4). Some observers report a bradycardia (5). Meningismus, most often seen as a "stiff neck", is very common and may proceed to actual meningitis with spinal fluid fiindings (6). The European observers, who have had much more experience with this disease than those of us here, consider the meningeal expressions as quite constant; Costa and Trosier divide them into three types. Type I consists of the usual course of Weil's disease with headache as a sign of meningeal irritation and meningitis as a complication; type II consists of meningitis with moderate jaundice; and type III is a pure meningitis with no jaundice (7). Though some might disagree with this classification, it seems fair to say that the consensus of opinion is to accept meningeal symptoms as being quite constant.

This initial stage lasts about one week, and in it leptospira are found free in the blood stream. There are as yet no organisms in the urine and no circulating antibodies in the blood.

The second stage has commonly been called "icteric", but, as Jeghers and Houghton point out, it would be better referred to by some other title; they suggest the use of "toxic." In the opinion of the writer this term is not wholly satisfactory for it might also apply to the first stage. It is a far better terminology than "icteric" however, for it excludes jaundice as a requirement in making a diagnosis, which we have already referred to above. If jaundice does occur, it usually deepens slowly; the liver becomes larger, though remaining smooth, and splenic enlargement may or may not occur. In the severer cases there is a hemorrhagic tendency that may express itself in such varied ways as petechiae, epistaxis, subconjunctival hemorrhage, hemoptysis, melena, or hematemesis (1). The cause of this is unknown.

Renal function is definitely impaired. This is quite characteristic and aids in differentiating Weil's disease with jaundice from other forms of jaundice. There is often oliguria which may proceed to anuria; albuminuria is present and casts and red cells are found. The NPN level rises.

This stage also lasts about one week. When jaundice is present the disease is usually severe with a mortality of about 30%. Without jaundice, though the disease is milder, some authors claim that the incidence of meningitis is higher (8).

There are no longer demonstrable leptospira in the blood stream, but they may easily be found in the urine. Specific antibodies can be shown in the blood.

The third stage is a convalescent period; there is a moderate anemia and roughly 30% of the cases show an "after-fever" which lasts from 4 to 20 days (1). Naegeli considers this double peak fever as an almost constant accompaniment of Weil's disease; in this he represents the European view (4).

The pathological investigation of Weil's disease has not been very successful in demonstrating specific diagnostic lesions. The liver is grossly normal, smooth, firm, moderately enlarged; there is nothing characteristic of specific infection (8). It is often bile stained and is never shrunken as in acute yellow atrophy (1). Histologically it shows bile staining, cloudy swelling and leptospira. In attempting to explain the jaundice, Jeghers and Houghton offer two possible explanations. Either there is mechanical obstruction in the bile ducts from the swollen and edematous liver cells, or the cells themselves are so damaged that they cannot properly excrete bile (1). Meakins states that the Van den Bergh is indirect; this would not tend to favor the idea of mechanical obstruction (8). Lack of evidence compels us to leave the question unanswered.

Grossly the kidneys are somewhat swollen and bile stained. Microscopically they show necrosis of the convoluted tubules and interstitial infiltration. The glomeruli are unaffected. The renal damage is often extensive but is better estimated clinically and from laboratory tests than from pathological examination (1).

Capillary damage is extensive; there are minute hemorrhages all over the body, especially in the kidneys, pleura, peritoneum, and gastro-intestinal tract.

The calf muscles show no obvious damage in spite of the severe myalgia often present there. Histologically there may be a few scattered pinpoint hemorrhages and isolated fibers may show swelling, loss of striations, and hyalinization. This is not similar to the Zenker degeneration seen in typhoid which is visible grossly.

Though the spirochetes are for a time blood borne and are thus carried to all the organs, they are seldom found there after death. This adds to the difficulty of making a pathologic diagnosis of Weil's disease; only rarely is it possible (1).

The epidemiology of Weil's disease involves a consideration of the carrier rat problem, for since the disease was first recognized it was noted that the highest incidence was in those whose work made contact with rats possible. Butchers were especially susceptible, and during the World War it was common in the trenches. Epidemics were reported in the Italian, German, and French armies (9).

The causative organism of Weil's disease, the Leptospira icterohemorrhagica, is found in the urine of infected rats (10). Various attempts have been made, both here and abroad, to estimate the extent of this rat resevoir with somewhat conflicting reports. Jeghers and Houghton state that about 10% of the rat population of the United States either harbor or excrete the spirochete (1). In an epidemic of jaundice in Albany, N. Y., 28 of 128 rats collected from the area showed leptospira which caused jaundice and hemorrhage in the guinea pig (11). This particular epidemic traveled very rapidly through a hospital there, and clinically the patients exhibited the signs and symptoms of Weil's disease, but blood cultures were repeatedly negative and the organism was not conclusively demonstrated. In Scotland leptospira were found in the kidneys of 27.3% of 117 rats collected at random, with a higher level of infection in older rats (11). In Antwerp 48% of 100 dogs at the city pound showed leptospira antibodies (12). Here again there was more infection in the older dogs.

Man is infected by contact with soil or food contaminated with urine from infected rats; the leptospira apparently are able to penetrate the

unbroken skin and can also enter by way of the gastro-intestinal tract (10) (1) (8).

Since animal infection with the spirochete is so common, interest naturally centers around the distribution of the spirochete itself. It was discovered that the Weil's organism is not the only pathogen in the leptospira group; Leptospira canicola, found in dogs, causes no jaundice in man, but does cause prominent meningeal symptoms (11). Leptospira grippo-typhosa is the cause of Swamp Fever found in central Europe, while Leptospira hebdomadis is the causal organism of Seven Day Fever in Japan (1). This year Vagn and Mortensen reported a case of Weil's disease with a typical serology that was found to be caused by a rare strain of Leptospira sejro (7). How widespread these organisms are is realized when one considers the fact that representatives of the group have been found in pond water, mud, garden soil, puddles, sewers, resevoirs, salt springs, sea water, tap water, and in 87.5% of samples of drinking water from 47 New England cities (1)!!

The incidence of the disease is higher in Europe than in the United States. In the nine years following the year 1924 there were 452 cases reported in the Netherlands. In France where a Weil's agglutination is common procedure, 23.1% of 1233 blood samples collected in one year gave positive results (1) (9) (7) (13). In the United States since the first established case was reported in 1935, additional cases have been appearing sporadically; Blake mentions 37 in the five year period that has elapsed (2). It is possible that this figure will become larger with increasing consideration and better recognition of the condition.

The disease has been recognized as a compensable industrial hazard in London, and more recently in New York. Butchers, fish cutters, sewer workers, and miners are most open to infection (1) (14).

The diagnosis of Weil's disease should be made in the first stage rather than in the second as commonly happens, for it has been shown that the efficiency of treatment decreases as the disease progresses (10). An abrupt acute infectious process together with myalgia, of uncertain origin, occurring usually in an adult male, should raise the question of Weil's disease. Once the possibility of Weil's disease is entertained the final diagnosis becomes largely a laboratory problem with confirmatory evidence available clinically. During the first week guinea pigs may be injected with blood from suspected Weil's patients; if positive the pig dies in 10-12 days and should be autopsied. Recently a note of caution has been sounded in respect to guinea pig inoculation by Greene-Farrell who advises that the pigs used weigh less than 175 grams and that subinoculations from pig to pig be done; the first animal is often negative while the later ones give good positive reactions (11).

In this stage dark-field examination of the blood should also be attempted and blood culture on special spirochete media can be tried, but main reliance should be placed on the guinea pig inoculation.

In the second week the urine should be examined for spirochetes, and after centrifuging should be injected into a pig as above. Since there are now antibodies in the patient's serum they may be used to agglutinate known cultures of leptospira and the titer noted. Agglutination should be tried not only with Leptospira icterohemorrhagica but also with Leptospira canicola (11). Again the more recent investigators give warning; Brown and Broom report that the antigens often act peculiarly, in that formolised cultures are not agglutinated in as high a titer as unformolised ones and that microscopic agglutination techniques may often miss low titer serums (15). For the above serologic tests samples of the patient's serum should be sent to Washington, D. C.

In the differential diagnosis care must be taken to separate this acute infectious jaundice from other types. As Proger points out, Weil's disease is a type of infectious jaundice, but not all infectious jaundice is Weil's disease (3). Many epidemics of jaundice have occurred in which Leptospira have never been isolated; these are usually benign and highly contagious. Their etiology is unknown. They occur chiefly in the fall and winter, affecting chiefly children and young adults. They are non-fatal and show no renal hemorrhagic findings as does Weil's disease (17).

(*Continued on page 60*)

Development Fund

by ELDREDGE M. HILLER, *Assistant to the Dean*

In the last issue a generous gift of $25,000 to the building and endowment fund was reported by Dean Stearns and Mr. Ira Rich Kent. Shortly thereafter, a $25,000 pledge was reported by Dr. Sara Jordan. The latter has been made by a prominent industrialist and his wife in Boston. Additional gifts of lesser amounts have come from individuals in Maine and Rhode Island, as well as Massachusetts, placing the total of the fund over $425,000.

A second announcement of great potential future interest is that a weekly magazine of national circulation has expressed a definite interest in Tufts' program of training and medical services for New England. A representative of the magazine, in coöperation with the writer, has made an initial survey of the Medical School and its clinical teaching centers. Several visits to doctors in rural communities have been made to see the physician at work under actual conditions of his practice, and particularly to understand the life of a typical family doctor. The program of postgraduate refresher courses, hospital extension services and diagnostic aid were seen in operation at the New England Medical Center. Picture possibilities are being discussed; and if any students care to jot down and send in any ideas further to attract the interest of this magazine, they will be welcome. Suggestions which depict some tangible aspect of teaching, research, or point to the problems involved in general practice, are invited.

Activities on behalf of specific financial objectives produce many beneficial side results. Some are as important if not more so to the institution and its personnel than the original objectives themselves. Since Tufts has started its campaign for building and endowment, it has attracted for teaching and research nearly $100,000 from foundations, gifts for library endowment, and gifts for other purposes. Another side result has been that of wills, and at least one bequest of $15,000 for scholarship endowment is known to have been written into the will of an interested anonymous woman donor in Boston. Several lawyers have asked the School for literature for unnamed clients.

The grants from foundations include two appropriations from the Rockefeller Foundation, made last winter through President Carmichael, for teaching and research in psychiatry and for research on certain aspects of the brain; two grants from the Dazian Foundation; and one from the Markle Foundation. Included also is an earlier gift which has been of widespread benefit to students taking clinical work under the Department of Medicine at the Boston City Hospital. This is the well-known grant of $35,000 from the Charles Hayden Foundation. Mentioned in this journal editorially last year, it has made possible the establishment of an excellent clinical teaching arrangement at the City Hospital. Under Dr. Cadis Phipps there is a full-time supervisor and four teaching assistants. Third and fourth-year students have commended the close supervision, individual instruction and careful selection of cases suitable for demonstration resulting from this set-up.

New Charles Hayden Memorial Scholarships

Mr. J. Willard Hayden, President of the Charles Hayden Foundation, has just awarded a grant of $10,000 to the Tufts College Medical School for scholarships for selected members of the entering class next autumn, it was announced on December 26 by President Leonard Carmichael. Following the regular plan of the Charles Hayden Memorial scholarships in other institutions, a portion of the total sum will be used for outright scholarships during the first year of medical study and a portion held as a special loan fund for these same students in their upper class years. More complete announcement will be made as soon as a committee is appointed and details of administering these scholarships are worked out.

Alumni News

Tufts College Medical Honorary Society

The Tufts College Medical Honorary Society has formulated plans for its second annual clinic day to be held Wednesday, January 15, 1941, at the New England Medical Center in the auditorium of the Pratt Diagnostic Hospital. The clinic this year will be devoted to Cardio-renal, Gynecological and Obstetrical subjects. All medical students and alumni are invited to attend these clinical lectures in the morning. The program is as follows:

8:45- 9:15—Registration.
Each member will be required to register.

9:20- 9:40—Clinical Picture and Treatment of Angina Pectoris.
Dr. Joseph H. Pratt.

9:40-10.00—Some Urological Problems in Children.
Dr. Harold Chamberlin.

10:00-10:20—Coronary Disease and its Treatment.
Drs. Schlesinger and Blumgart.

10:20-10:40—Etiological Factors in Hypertension in relation to the results of Partial Sympathectomy.
Dr. Robert Palmer.

10:40-11:00—Discussion on the Treatment of Cardio-Renal Disease.
Dr. Albert H. Horner.

11:00-11:20—Indication for Caesarian Section.
Dr. Louis E. Phaneuf.

11:20-11:40—The Use of Hormone Extracts in Sterility.
Dr. Charles H. Lawrence.

11:40-12:00—Management and Treatment of Habitual Abortion.
Dr. Alonzo K. Paine.

12:00-12:20—Office Treatment of Gynecological Conditions.
Dr. Maurice O. Belson.

12:20-12:40—Dysmenorrhea and its Treatment.
Dr. Joe V. Meigs.

12:40- 1:00—Ovulation Problems.
Dr. John Rock.

1:00- 1:15—The Electro Encephalo Shock Machine. A practical demonstration.
Dr. Louis Feldman.

The annual dinner will be held on Wednesday evening, January 15, 1941, at the University Club, Boston, at 7 P. M. sharp. The guest speaker of the evening will be Dr. Emil Novak, of Baltimore, Maryland, a clinician and recognized authority on Endocrinology. His subject will be, "Gynecological Problems of the Adolescent Girl."

Annual Dinner Committee

The annual dinner committee is to be headed by Dr. Philip E. Meltzer as chairman. He will be assisted by Doctors Ober, Heffernan, Bearse and Manary.

Nominating Committee

The nominating committee for the Alumni Council for 1941 will have Dr. William Browne as chairman. He will be helped by Doctors Joslin and Appel.

Doctor's Symphony

Dr. Julius Loman (Tufts '25), President of the Boston Doctors' Symphony Orchestra extends a cordial invitation to all medical students and doctors who play an orchestral instrument and are interested in joining this orchestra to get in touch with him at 1284 Beacon St., Brookline, Mass.

Editorially Speaking

The Tufts Medical Journal is embarking on a new venture . . . it is conducting a student curriculum survey.

A committee of four (Barry, Copel, Freedman, Thomas) has been selected from the editorial staff and they have arranged and mimeographed a six page questionnaire on the curriculum of the first two years based on a questionnaire gotten up during the summer by a committee appointed by the Association of Medical Students at Tufts. With the disintegration of the AMS at Tufts this questionnaire they had prepared was left without a sponsor. The Staff of the Tufts Medical Journal felt that a student curriculum survey could be of help to the faculty in their consideration of curriculum problems and has therefore taken over this questionnaire, enlarged and modified it. It has now distributed these sheets to the present second and third year classes.

This first survey is really in the nature of a trial balloon to find out what curriculum problems are troubling students in the first two years and how mature an evaluation of these problems might be expected. If successful, this questionnaire is to be followed in the future by other questionnaires and it is planned to extend the scope of the questionnaires so as to cover the third and fourth years.

All students interested may submit questions for inclusion in future questionnaires to any member of the Journal Staff, and anyone interested in this type of work will be enthusiastically welcomed by the committee if he will get in touch with the committee and inform them of this fact.

The questionnaire method of approach to the problem was adopted so that the Curriculum Committee shall be able to report the opinions of the students on curriculum problems rather than merely the opinion of the committee itself.

The committee is willing also to serve as a clearing house and secure an accurate and complete expression of student opinion on any aspect of the teaching of a course about which the head of a department desires to ascertain student opinion. All such questions will be included if forwarded to the Editor, Tufts Medical Journal, 416 Huntington Ave., Boston.

The attention of all students desiring to submit papers to the Journal is called to the fact that the deadlines for the third and fourth issues of the Journal will be February 15 and April 15 respectively. No papers submitted after April 15 will be eligible for consideration for the G. F. Keenan Memorial Award of $25 presented by the Tufts Medical Alumni Association or the New England Journal of Medicine prize of a year's free subscription to the NEJM.

* * *

Excerpt from Article II Section 5 of the By Laws of the Student Activity Plan of Tufts Medical School: "The Editor-in-Chief of the Tufts Medical Journal shall be chosen by the Dean in May of each year from a group of students who shall apply to the Dean in writing and who shall submit competitive essays in order that their qualifications as Editor-in-Chief may be properly evaluated.

Alpha Omega Alpha

On Monday, December 2, the Tufts College Medical School Beta chapter of Alpha Omega Alpha, national honorary medical society, was officially installed at Crane Chapel in Medford.

Charter Faculty Members included: Dr. David D. Berlin, Prof. of Clinical Surgery; Dr. Abraham Myerson, Professor of Neurology, Emeritus; Dr. Dwight O'Hara, Professor of Preventive Medicine; Dr. Alonzo K. Paine, Professor of Obstetrics; Dr. Louis E. Phaneuf, Professor of Gynecology; and Dr. A. Warren Stearns, Dean and Professor of Neurology.

Student Initiates included ten members of the class of 1941: Carl J. Antonellis, Carroll Bryant, Jr., George A. Dodge, 2nd, Clement S. Dwyer, Jesse G. Garber, Herbert F. Hager, Alfred Kant, Arthur N. Kelley, John L. O'Hara, and Raymond Yesner.

Following the addresses the student initiates convened for an election of officers and to vote that former members of the Sir William Osler Society be granted membership in the newly formed chapter of Alpha Omega Alpha. Officers elected were as follows: Alfred Kant, President; Arthur N. Kelley, Vice-president; Carroll Bryant, Jr., Treasurer; and George A. Dodge, 2nd, Secretary.

The Role of Iodine in the Thyroid Gland and Thyroid Function

by Leopold M. Trifari, B.S.

Introduction

The earliest studies on the Thyroid gland began in 1874 with the publication of Gull's article (18) describing the cretinoid state. Previous to this, any mention of the function of the thyroid gland was entirely speculative or completely confused with the parathyroid glands. In 1878, Ord (19) renamed this cretinoid state myxedema, believing that the thickened brawny skin was due to mucin deposits beneath the skin. A few years later, the Reverdin brothers (20) in 1882 and Kocher (21) in 1883, gave fuller reports concerning surgical thyroidectomy and its sequalae in the treatment of goiter. The condition was called cachexia strumipriva and Kocher recognized it as being identical with Gull's myxedema.

Following these reports, Schiff (22), working on dogs, and Smith (23), working on cats, subjected these animals to thyroidectomy and produced the acute symptom-complex of tetany, following which operation the animals died in a week. Rabbits, sheep and goats, it was noted however, lived for indefinite periods with no such acute symptoms. But it was not until 1891, when Gley (24) discovered the external parathyroids in the rabbit, that real separation of the thyroid and parathyroid physiology was accomplished. Recent work of Aub (17) and his co-workers has proven, however, that an interrelationship exists between these two glands in regard to calcium and phosphorous metabolism. Since this time, many species of animals have been subjected to thyroidectomy to produce essentially identical conditions of myxedema in all these animals.

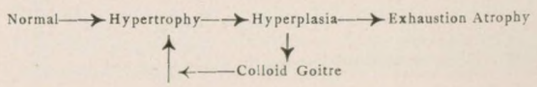
Since 1820, when Coindet (25) first demonstrated the therapeutic value of iodine in the treatment of goiter, the association of iodine and thyroid has been suspected. His observations made it possible to establish that iodine was the active agent in the remedies such as seaweed, salt, etc., that had been used for centuries for the treatment of goiter. It was in 1895 by the efforts of Baumann (26) that iodine was proven to be a normal constituent of the thyroid gland.

The Anatomy of the Thyroid Gland

It is wise here to include a brief discussion of the thyroid anatomy, merely to point out a few salient facts of importance. Marine (15) emphasizes the important points as related to the offering of a good background for the discussion of thyroid disorders. The thyroid gland ancestrally belongs to the ailimentary tract and is endowed with tremendous capacities for increasing or decreasing its activities as indicated by changes in weight, micro-appearance, iodine content and blood supply. While hyperplasia of the gland indicates a hyper-activity, it does not necessarily mean hyperfunction. Reinhoff (27) in 1924 suggested that the lymphatic system of the gland is a closed one and not involved in the transmission of the specific secretion of the gland.

Vesicle formation and colloid storage increase till birth, followed by a period of rest shortly after birth, and then renewed activity. At puberty the gland exhibits its greatest activity and here colloid storage is at a minimum level. Later, the colloid store progressively increases while the gland is relatively inactive normally, till about the 50th year, after which retrogression goes on. The resemblance of the gland of the human adolescent to that regarded as characteristic of Grave's disease is pointed out by Cooper (28).

Because of this wide range of anatomical changes that may occur, Marine (9) has been able to establish an anatomic cycle represented schematically as follows:



This cycle is well-known and needs no further explanation, except to point out a few interesting facts. The actively hypertrophic and hyperplastic stages indicate stimulation of the gland cells and, as far as is known, this is brought about solely by the action of the thyrotropic principle of the anterior pituitary gland. The colloid state represents the return of the hyperplasia to the normal or quiescent condition. It is quite probable that changes occurring in the thyroid in simple goiter or in exophthalmic goiter or even in the compensatory hypertrophy after partial thyroidectomy are essentially normal i.e. merely phases in the Marine cycle. This is as yet a debatable point among clinicians, some feeling that certain clinical states are manifestations of dysfunction and not a hyper or hypofunction.

The Biochemistry of Iodine

Following Baumann (26), who showed that iodine was an essential component of the gland, Hutchinson (29) later in 1896 concluded that the iodine was in the colloid and as such, in combination, it was the active agent of the gland. Ostwald (30) in 1897 confirmed this and found the combination to be a globulin, naming the extract thyreo-globulin. He showed also that 95% of the thyroid iodine was in such a combination. Further he proved that the iodine of the gland varied directly with the amount of colloid present. Marine and Williams (31) in 1908 demonstrated that the iodine varied inversely with the degree of hyperplasia of the gland cells. The maximum store of iodine is between 5 and 6 mgm. per gram of dried tissue while the minimum amount may be an inestimable trace: truly a wide variation and in confirmation of the anatomical changes that occur. The figures representing the iodine content are interesting to note. These are from Marine (31):

Normal	2.17 mgms.	per	gram	dried	tissue	
Hyperplastic	0.71	"	"	"	"	"
Colloid	2.00	"	"	"	"	"

The close resemblance of iodine content in the normal and colloid stages is further indication of the similarity of these two stages.

On Christmas day in 1914, achieving a goal sought by many investigators since first Baumann showed iodine was in combination as the active agent of the gland, Kendall (32) crystallized thyroxine from the extract of the thyroid gland. It was found to contain over 60% of iodine. But it was not until 1926 that Harington (33) was able to give it its correct formula. This thyroxine was later synthesized by Harington and Barger (33) in 1927. These workers also isolated diiodotyrosine from the gland extract and evolved its formula. They feel that thyroxine is formed in the thyroid from tyrosine through the stage of diiodotyrosine and hence conclude that varying ratios of these two iodine-containing substances are to be expected in the gland. This has been found to be true by Leland and Foster (34), by Kendall (32) himself, and others. This varying ratio between the amounts of thyroxine and diiodotyrosine is quite comprehensible if one recalls that the iodine available is that which is provided in the diet, which differs in different areas and with different types of diet. It is also understandable in view of the varying stages of the gland in the Marine cycle, a point determined by the response of the environment. It is also to be noted that no fixed proportion of diiodotyrosine radicals is changed to thyroxine radicals at any stage of the gland. There is some evidence that proteases can non-specifically bring about the change of tyrosine to thyroxine. This is probably a specific reaction of the thyroid gland because, while mere iodinization of proteins will give diiodotyrosine radicals, it will not give thyroxine unless enzymes are present (13).* As yet there is no direct evidence to suggest that any specific enzyme exists which may be involved in this reaction. Normally, it has been estimated that 60% of the thyroid iodine belongs to diiodotyrosine radicals and the other 40% to thyroxine radicals (33).

---

*However two recent papers by Mutzenbecher (Z. physiol. chem. **261**:253, 1939) and Ludwig + Mutzenbecher (Z. physiol. chem. **258**:195, 1939) disagree with this concept of Lerman + Salter as they were able to isolate thyroxine after incubating iodized horse serum or pure di-iodotyrosine with dilute alkali at 37.5° for one to two weeks.

While some of the iodine of the body is in the thyroid gland, estimable amounts have been found in other organs also, especially the ovaries, pituitary gland and the diencephalon. It is found in the blood in quantities of about 10 gamma per 100 c.c. As a matter of fact, only one-fifth of the total body iodine is in the thyroid gland. Due to the physiological relationships that exist among the anterior pituitary, the ovaries and the thyroid, any iodine there could very well be of thyroidal origin.

The Physiology of Iodine

It is generally considered that the normal function of the thyroid gland is causatively linked with the oxidative processes of the body cells. This seems logical in view of Magnus-Levy's (35) original observation in 1985 that in myxedematous patients the metabolism was greatly reduced and that treatment with desiccated thyroid raised the level to normal and above, and also by later observations that thyroidectomy in animals was followed by a depression of heat production and the opposite effects from thyroid feeding.

The question then arises as to which of the iodine substances is the essential principle of the gland and what are their relations to one another. This last question has been partially answered by Harington's theory of thyroxine formation. Recent studies, especially with iodized proteins, have complicated the former issue even further.

Qualitatively, thyroxine satisfys all the criteria we can apply to decide what is the active principle of the gland. Quantitatively, there is great doubt as to whether it does so. Desiccated thyroid restores thyroidectomized animals to normal even when given orally. Thyroxine does the same, but in other tests, especially the oxygen-consumption test, pure thyroxine is less active than mixtures of thyroxine and thyroxine-peptide which Harington (36) obtained by enzymic digestion of the gland. Diiodotyrosine and thyronine are inactive. Certainly, none of these other substances equal thyroglobulin in activity (36).

Using the acetonitrile test, which is done by noticing the increased resistance of mice to acetonitrile poisoning after thyroid feeding, Reid Hunt (37) showed that the activity of different thyroid preparations depended upon the iodine content. Thus, thyroid gland and thyroglobulin are equally active orally but have no action given intravenously. Diiodotyrosine is inactive whereas thyroxine is about two-thirds as active as thyroid gland.

Clinically in myxedematous patients, diiodotyrosine shows no activity while thyroglobulin and thyroxine are equally active qualitatively. Thyroxine with peptides is equal to thyroxine alone in activity (13).

The active iodine compound in the blood behaves as if it were a protein, giving anaphylactic results. This is further indication that thyroxine is not the active principle.

Further proof that thyroxine is not the active agent but that the iodine content of the principle is the deciding factor is given by Lerman and Salter in their paper in 1939 (13). They iodized proteins and found that they had one-fifth the activity of soluble thyroid and one-four hundredth the activity of iodine alone, when these preparations were given to myxedematous patients.

As the matter stands at present, there is no need of assuming the existence in the thyroid of any active principle other than those determined by iodine and thyronine, the basic radical of the crystalline principles extracted from the thyroid. The combinations of these substances are really active principles that confer specific properties on a more or less complex protein fragment (19). This opinion is supported by the work of Harington and Salter (38) who have demonstrated thyroxine-combined peptides are more active than thyroxine alone. It is the explanation of this phenomenon that is now pressing the ingenuity of research men.

One other factor not yet mentioned in thyroid physiology is the relation of the pituitary body. Thomson and Collip (11) have reviewed the evidence of this relationship recently. Following the method of Anderson and Collip (12) in the preparation of thyrotropic principle, it has been shown that the injection of this extract causes hyperplasia of the thyroid with a loss of iodine from the gland and an increase in the blood iodine and a picture of the hyperthyroid state. Evidence is fairly conclusive that the thyroid gland is stimulated by this principle of the anterior pituitary. It is known that exophthalmos is due to both thyroid and anterior pituitary relationships. One significant fact is that exophthalmos cannot be produced after the sympathetic pathway to the eye is divided (40). It is believed to depend on the stimulation of sympathetic centers in the central nervous system, probably the hypothalamus. The high iodine content of this part of the brain is probably important in this phenomenon.

Many workers, such as Abderhalden, Meyer, Mansfield, Cannon and others, have emphasized these interrelations especially in regard to the place of action of the active principle of the thyroid gland.

Iodine in Thyroid Disease

With this basis, let us consider the value of iodine in thyroid disease and how its proper and judicious use can be accomplished to gain effective clinical results.

Clute and Pilcher (2) reviewed 121 cases of thyroid disease in the Lahey clinic and studied the use of iodine in these cases, comparing the patients studied with 152 cases of thyroid disease a year later. They have come to a series of conclusions which I should like to consider separately.

Iodine is of generally recognized value in the prophylaxis of endemic goiter. Only minute quantities are necessary for this use since one need only supply the small amounts that the individual usually obtains from his drinking water or his table salt. Their method of giving iodine is to use a chocolate-coated tablet containing one-sixth of a grain of iodine. This tablet is given once a week to children, especially female children, in goitrous areas about a year or so before puberty changes are expected to occur and continued all through this period and for a year after sexual function is well established.

The place of calcium in goiter development has recently been studied. It has been known for a long time that the excessive intake of calcium increases the effect of a goiter-producing diet. Abelin (42) has shown that calcium lessens the metabolic effects of thyroxine; an antagonism exists—whether actual or apparent is as yet unknown. It is also known that a high phosphorous and low calcium diet can cause a goiter, even with adequate iodine administration. How, it is not known. There is no doubt that the efforts of Aub (17) and his co-workers will go far towards the explanation of this observation.

In regard to the rationale of iodine therapy as applied to endemic goiter, Marine (15) makes a few extremely interesting statements. He believes that as yet, since there is no evidence to indicate that the ability of the thyroid to build up thyroxine and diiodotyrosine from tyrosine is impaired in a goitrous gland, one must still conclude that simple goiter is an iodine-deficiency disease, the deficiency resulting from one or more of the three following factors:

1. Increase of body needs—as seen in puberty, pregnancy, menopause, infections of the body and excess of certain substances in the body.
2. Interference with the absorption or utilization of the normal intake of iodine.
3. An abnormally low intake of iodine.

All the factors in #1 are in reality only relative deficiencies of iodine and as soon as the increased demand is over, the use of iodine is no longer indicated. How this is determined is beyond the scope of this paper.

The other 2 factors are absolute deficiencies. As regards the one of failure of absorption and utilization, speculation alone holds the stage for there is no knowledge. Their existence as factors is not even proven.

In the case of a low intake, the result of giving iodine seems truly a physiological one. Marine (15) points out, however, the danger of giving iodine over protracted periods to cases believed to be goiter but actually susceptible or latent exophthalmic goiter presenting adenomatous goiters. This, he believes, gives rise to the so-called iodine-Basedow's disease, as Means (1) of Boston also believes. Iodine use here can be diagnostic, as Means (10) has pointed out, by noticing the change in the B.M.R. following iodine administration. Characteristic curves result depending upon the true condition. It is

wise to remember that in this diagnostic use of iodine a single B.M.R. test is of no value but must be repeated frequently. Space limitations prevent any discussion of these curves.

Clute and Pilcher (2) point out also the advisability of giving a pregnant woman with endemic goiter iodine therapy to prevent among other things the hyperplasia of the thyroid in the expected child.

Iodine therapy is also indicated in hyperthyroid states, thyrotoxicosis or toxic goiter. Clinicians are quite in agreement that its value is involved only in the pre-operative management of such an individual. There are still various differences as to the duration of the treatment and the dosage of iodine given, but they are all essentially similar. Its value in a thyroid crisis of a toxic patient is uniformly agreed upon by all authorities, especially in the prevention of such an attack. The pre-operative use of iodine is intended to abolish the hyper-functioning of the gland. *The response to iodine has come to be looked upon as a cardinal manifestation of the disease.* Means (1) stresses this point especially in the atypical cases of thyrotoxicosis. He even feels that the iodine response will aid in determining the prognosis of these cases.

Adequate dosage to attain full iodinization of patients with toxic goiters is contained in 5-10 minims of a saturated solution of potassium or sodium iodide, given once daily for 7-14 days. It may be given by any route, the effect is always alike. It makes no difference what preparation is used, iodine acts as iodine no matter what combination or portal of entry is used.

The precise action of iodine in Grave's disease will probably remain unknown until more is known of the nature of the disease itself. If the disease is extra-thyroidal in origin, it is quite possible that the effect of iodine is also extra-thyroidal. The untreated gland in this disease is colloid-poor and iodine-poor, while following iodine administration, it tends to become colloid-rich and iodine-rich, i.e. it tends to return to the quiescent or resting stage as Baker (43 and Curtis et al (6) have shown. Lately, Loeser and Thompson (14) feel that in response to the presence of ionic iodine in the blood, the hypophysis varies its production of the thyrotropic principle and thus in turn the output of the thyroid is varied, a process which in itself may utilize or detoxify iodine. If this is true, then the iodine administration may retard the thyroid gland from producing thyroid hormone and thus cause the clinical response seen in toxic goiter.

Also involved are the blood and urine iodine values that occur in such patients. Curtis (6) feels that the significance of the blood iodine values is similar in this disease to that of the blood sugar in diabetes and to the blood calcium in parathyroid disease. Certainly these values vary fairly uniformly with thyroid function, being elevated in hyperfunction and depressed in hypofunction and always elevated in iodine administration. Perkin and Catell (7) go even further and advocate that the level of the blood iodine pre-operatively is an index of the amount of thyroid to be removed at operation. The bad feature of this is that the determination of iodine by laboratory methods is a debatable technique among biochemists and, while fair agreement in values has been obtained, variations are still too great in view of the accuracy needed for such a procedure. Also, the determination of iodine is still an elaborate research technique. Here is a definite benefit which further research can make available to the clinician.

It has been noted that some post-operative cases of toxic goiter tend to remain toxic or to show recurrences. Iodine is of no value in the prevention of recurrences but does help the patient who remains toxic.

Means (1) blames the toxic state in this disease to the thyroid allowing the escape of thyroxine too fast—it "leaks" as he expresses it and hence the hyperthyroid state. Iodine, he claims, sets up an obstacle to this "leak" but only temporarily. Clinical evidence is certainly in favor of this theory. Let us remember that with iodine therapy the blood iodine values are elevated and that this increase may act in such a way as to stop the production of the thyrotropic hormone, with the resultant cessation of stimulation of the thyroid. This, Thompson (11) believes, to be the obstacle to the thyroid "leak". The simplicity of this explanation is too enticing but consistent with clinical evidence. Its greatest drawback is that it completely disregards the other endocrines.

Iodine therapy is not a cure for toxic goiter; it is merely a palliative measure. In view of this, let us consider now, briefly, the limitations of iodine administration. Clute and Pilcher (2) point out that no harm comes to patients with toxic or non-toxic adenomas by continued iodine therapy. But they emphasize the waste of time that occurs by relief with such measures only. They claim that such a delay may be actually dangerous as the adenoma may prove malignant. This point is well-taken since 95% of thyroid malignancies arise from adenomas. Hence they rightfully claim that surgery is the treatment of choice. Also the reduced state of the tumor that occurs with iodine therapy is temporary and it will regrow at a later date.

Another important limitation to iodine therapy in toxic states is that the longer the state of hyperthyroidism lasts, the greater is the danger of a thyroid crisis and the worse a risk the patient becomes for surgery. The incidence of one-stage operations for total thyroidectomy is now on the increase in the Lahey clinic by the more judicious use of iodine pre-operatively (2).

I would like to express my gratitude to Dr. A. Canzanelli who made his references available to me for the preparation of this paper.

BIBLIOGRAPHY

1. Means and Lerman, JAMA, **104**: 969, 1935.
2. Clute and Pilcher, NEJM, **210**: 117, 1934.
3. Harington, Lancet, page 1199, 1935.

4. Harington, Lancet, page 1261, 1935.
6. Curtis et al, JAMA, **101**: 901, 1933.
7. Perkin & Catell, J. Clin. Invest., page 18, 1939.
9. Marine, Lecture Delivered at Ohio Univ., 1938.
10. Means, Ann. Int. Med., **7**: 439, 1933.
11. Thompson & Collip, Arch. Int. Med., **45**: 261, 1938.
12. Collipetal, Ann. Int. Med., **8**: 10, 1934.
13. Lerman & Salter, Endocrin, **25**: 712, 1939.
14. Loeser & Thompson, Internat. Clinics, **3**: 149, 1935.
15. Glandular Physiology & Therapy—Symposium ppd. by Council of Pharmacy AMA, 1935.
16. Recent Advances in Endo., Cameron, 1940.
17. Aub et al, J. Clin. Invest., **7**: 97, 1929.
18. *Gull, Tr. Chir. Soc. Lond. **7**: 180, 1874.
19. *Ord, Med. Chir. Trans. Lond. **61**: 57, 1878.
20. *Reverdin & Reverdin, From Marine's Article (9).
21. *Kocher, Arch. F. Klin. Chir. **29**: 551, 1883.
22. *Schiff, From Marine's Article (9).
23. *Smith, Anat. Rec., **2**: 57, 1916.
24. *Gley, C. R. Soc. Biol., **43**: 551, 1891.
25. *Coindet, Ann. de. Chym. et Phys., **15**: 49, 1820.
26. *Baumann, Z. Physiol Chem. **21**: 319, 1896.
27. Reinhoff, Monograph-Medicine, **10**: 257, 1931.
28. Cooper, From Marine's Article (9).
29. Hutchinson, J. Physiol, **20**: 474, 1896.
30. *Ostwald, Z. Physiol Chem. **23**: 265, 1897.
31. Marine & Williams, Arch. Int. Med., **1**: 349, 1908.
32. *Kendall, Collected papers of Mayo Clinic, **8**: 513, 1916.
33. *Harington & Barger, Biochem, J., **21**: 169, 1927.
34. Leland & Foster, J. Biol. Chem., **95**: 1931.
35. *Magnus-Levy, Berl, Klin. Woch, **32**: 650, 1895.
36. Harington & Barger, Biochem. J., **24**: 456, 1930.
37. *Reid Hunt, Am. J. Physiol, **63**: 257, 1923.
38. Harington & Salter, Biochem. J., **24**: 456, 1930.
40. Cannon et al, Amer. J. Physiol, **72**: 283, 1927.
42. *Abelin, Biochem, Ztschr, **199**: 72, 1928.
43. Baker, From Reference No. 10.

*Abstract of article used.

Announcement

The Trustees of The New England Journal of Medicine will award one full year's subscription of The New England Journal of Medicine to the student whose original contribution to The Tufts Medical Journal during the 1940-1941 school year is adjudged best. The winner will be announced in the May issue of this Journal.

THE

GEORGE F. KEENAN MEMORIAL AWARD

OF

TWENTY-FIVE DOLLARS

PRESENTED BY THE

TUFTS MEDICAL ALUMNI ASSOCIATION

FOR

THE BEST ORIGINAL STUDENT PAPER APPEARING

IN THE

TUFTS MEDICAL JOURNAL

during the 1940-1941 school year

Announcement of the winner will be made in the May issue of the Journal

Book Reviews and Abstracts

Books

BACILLARY AND RICKETTSIAL INFECTIONS, Black Death to White Plague, by W. H. Holmes; first edn.; 1940; Macmillan; 676 pages; $6.00.

Dr. Holmes writes for those to whom the practice of medicine is not a trade but a profession. His treatment of the subject is unconventional in comparison with the average textbook treatment of the same, but to this reviewer's mind it is very much more interesting and effective. The book covers the plague, tularemia, the Rickettsial diseases, undulant fever, cholera, typhoid and the paratyphoids, the dysenteries and related conditions, diptheria, botulism, tetanus, pertussis, flu, leprosy, TB and a few other miscellaneous bacillary diseases.

The author takes a broad view of disease and writes with an easy lucid style that makes this the type of book a student or practitioner can sit down of an evening and read and read without tiring. One learns a tremendous amount about the diseases in question yet one reads on as easily as if this were a novel rather than a textbook. Each disease is made a fascinating story which marches through the ages . . . a story in which are interwoven history and literature together with bacteriology, pathogenesis, diagnosis and prognosis.

Refreshing, stimulating, fascinating, instructive, up-to-date and accurate, . . . this book is recommended without reservation to all students, general practitioners and specialists.

MANUAL OF THE DISEASES OF THE EYE by C. H. May; 16th edn.; 1939; Wm. Wood and Co.; 515 pages with 31 colored plates and 387 illustrations; $4.00.

Succinct, compact, accurate, well organized and easily understood, this book is recommended to all undergraduates and general practitioners. The diagrams, charts and photographs are well done and extremely helpful, and the type used in printing the book is very easy on the reader's eye. All in all the diseases of the eye are covered with such a clarity of arrangement and text as to make this a handy and dependable guide to ophthalmology.

OBSTETRICS AND GYNECOLOGY by the Departmental Staff of the University of Chicago and other contributors and edited by F. L. Adair; 2 octavo volumes totalling 2031 pages with 663 engravings and 25 plates; first edn.; 1940; Lea & Febiger; $20.00.

These two volumes are an attempt to bring together the aspects of gynecology, obstetrics, physiology, biochemistry, research, general biology, sociology, pediatrics, general internal medicine and general surgery that may be applied to obstetrics and gynecology. Principles rather than details are stressed throughout. Over 60 physicians and biologists coöperated in this task and, as a result, even though a tremendous spread of material is covered by the books they are accurate and up to the minute. From the viewpoint of the student, however, it would have been more desirable to have devoted more space to obstetrics and gynecology and less to fields only distantly related to these two subjects, inasmuch as there are definite gaps in their coverage of the fields of gynecology and obstetrics.

The chapter and section headings are very ambitious, but in the attempt to cover many related fields completeness had to be sacrificed to a certain extent as far as each component part taken by itself is concerned.

This work is recommended for specialists in obstetrics and gynecology who are interested in the broader aspects of the field and in the experimental evidence behind many of the commonly employed principles in these fields.

PRACTICAL CLINICAL PSYCHIATRY by E. A. Strecker and F. G. Ebaugh; 5th edn.; 1940; Blakiston Co.; 728 pages with 57 illustrations and glossary; $5.00.

A concise and systematic presentation of the basic essentials of modern clinical psychiatry especially suited for the medical student and well adapted to the needs of the general practitioner who desires to bring his knowledge of psychiatry up to date. There is a minimum of the vague, intricate, impressive-sounding but underneath it all meaningless jargon found in too many books on psychiatry. It is a compact textbook of practical psychiatry written for physicians and not for theoretically minded psychologists, and the authors fully justify the use of the word "practical" in the title. The only criticism that the reviewer has is the briefness and oversimplification of the case histories sprinkled through the book. However methods of examination, diagnosis and treatment are adequately explained when one realizes that this book is really more of a manual of psychiatry than a comprehensive volume on all the phases of the subject.

TABER'S CYCLOPEDIC MEDICAL DICTIONARY Including a Digest of Medical Subjects by C. W. Taber and 14 associates; 1488 pages; 273 illustrations; F. A. Davis Co.; 1940; cloth, thumb indexed $3.00; plain $2.50.

Not covering as many words as the larger medical dictionaries like Dorland's, this dictionary attempts to cover the more common words and to do so more completely. However the main fault of this book is that it makes an effort to be a combined dictionary and textbook of medicine, of surgery, of nursing, of dietetics and of physical therapy. As a result not only is it not all of these but it is not even a complete medical dictionary that practitioners or medical students can use with complete confidence. However it does seem suited for the needs of nurses, technicians, medical secretaries and social service workers, and for these it is a well bound, extremely reasonably priced book.

HUMAN NATURE IN THE LIGHT OF PSYCHOPATHOLOGY by Kurt Goldstein; Harvard University Press, Cambridge, Mass., 1940; $2.50.

The William James Lectures, delivered at Harvard University in 1937-1938, and printed here for the first time, summarize the significant contributions made by Dr. Goldstein to neurology and related fields. Observations made on soldiers with brain injuries, during and since the last war help to clarify disorders of perception, certain aphasias, reflex changes and other neurological symptoms. Of even greater interest to the general practitioner is Dr. Goldstein's discussion of personality reactions. Excessive orderliness, rigidity of thinking, lack of imagination, and egocentricity may result from destruction of cerebral tissue. Reactions which may be described as "panic" (*Angst*) responses were also frequently observed in his patients. Similar reactions may appear in normal individuals, under conditions of stress, and their occurrence may be related to the development of such extreme reactions as certain types of epileptiform convulsions, or to the growth of Fascism among peoples swayed by insecurity.

The first chapter of this volume is entitled "The Holistic Approach", and presupposes some familiarity with general psychology and philosophy on the part of the reader. The average practitioner or medical student would, therefore, do well to begin by reading Chapter II. This is entitled "Pathology and Man's Nature" and contains illustrative clinical case material. It will serve, furthermore as a stimulating and readable introduction to the remaining lectures. The more difficult first chapter can then be saved until the end.

Dr. Goldstein is a gifted observer and profound thinker. This, his first publication since joining the Faculty of the Tufts College Medical School, merits careful study. A mastery of the psychological principles which he develops will result in a better understanding of one's patients and a clearer appreciation of the nature of man.

Abstracts

THE PANCREATICO-HEPATIC SYNDROME by Cole, W. H. and Howe, J. S.; *Surgery,* 1940; 8:19.

Up to the present time comparatively few records of typical cases of fatty liver and pancreatic fibrosis in adults appear in the literature. Five cases have been presented recently by various investigators, and a sixth is reported in the present article. A severe grade of fatty infiltration of the liver and fibrosis of the pancreas were characteristic of all six cases. Both experimental and clinical evidence indicated that the fatty infiltration of the liver was always secondary to a severe pancreatic insufficiency incident to a pancreatic atrophy and fibrosis.

The authors believe that the pancreatic steatorrhea of infancy and childhood is identical with the disease described more recently in the six adult cases. Both have certain manifestations in common, such as diarrhoea with foul bulky fatty stools, weakness, anorexia, nausea, vomiting, epigastric distress and loss of weight. Osteoporosis seems to be about the only symptom not common to both groups. Even greater similarity is seen in the pathological features of both of the conditions under discussion. The etiological factors in both are variable. In children three possible etiological factors may be responsible: congenital malformation of the ducts, fetal pancreatitis, and vitamin deficiency. In adults pancreatic stones or gall bladder disease may be responsible.

It now seems quite possible to make an accurate diagnosis of the condition with the clinical data obtained from a study of the six cases herein discussed. Laboratory tests, together with liver function tests and urine examination should prove helpful. Usually the blood cholesterol is below normal. A definite tendency toward a lowering of the blood protein level with a shift toward a reversal of the A:G ratio usually occurs.

One of the most helpful features in the treatment of the disease is lipocaic therapy. This may be even curative provided its administration is maintained at proper intervals. High carbohydrate and protein diets may prove helpful. The use of salyrgan and other drugs is indicated in symptomatic therapy.

PRESENT STATUS OF KNOWLEDGE CONCERNING INFLUENZA by Horsfall, F. L.; *A.J.P.H.;* 30:1302 (1940).

Numerous investigations seem to demonstrate that clinically indistinguishable epidemics of influenza are caused in some cases by a specific virus, influenza virus A, and in other cases by an unknown etiologic agent. The diagnosis of influenza A can be made only by laboratory tests involving recovery and identification of the virus from throat washings, or the titration of antibodies in the blood serum by a complement fixation or neutralization test.

Although several antigenic strains of influenza A virus have been demonstrated, it seems that humans infected with any strain develop a broad immunity to all strains. However, immunity is relative, not absolute, and varies with the antibody level. This level is maximal from about the 10th to the 30th day after infection. After 3 months only 75% and after one year only 40% of a small group studied had a sufficient antibody titer to be regarded as probably clinically immune. About 25% of persons exposed to influenza A show antibody response without clinical evidence of infection, which suggests they may play an important role as healthy carriers. Vaccines given parenterally to man stimulate antibody production, but their efficacy has not yet been definitely proven clinically.

Clinical Pathological Conference

(*Continued from page* 41)

asarca and uraemia are significant contributing factors which in turn, like the other findings, may be traced to the lesions within the kidney.

The author wishes to thank Dr. H. E. MacMahon for his assistance in the preparation of this report and Dr. Saunders for permission to use this case.

Benjamin Rush

(*Continued from page* 45)

vascular changes in the brain.

For many years Dr. Rush had suffered from a "pulmonary condition" which was tuberculous. More and more frequently he was forced to the sick bed, fuming with impatience until he was feeling well again when he would indulge in a burst of furious energy,—and the symptoms would return. In his later years the deadly disease took its toll of his vitality and sapped his vigor. On April 19, 1813, he died of a fulminating attack of his chest disease, composed and rational to the last and advising his son, Dr. John Rush, to "be indulgent to the poor."

This extraordinary man had played a great part in winning the independence of this country. He showed the way to American Medicine for years to come and made contributions of inestimable value to medicine, especially psychiatry. Honest to a fault and assured of the courage of his convictions, he quarrelled with almost all the important men of his day upon every conceivable issue. Conceited and overbearing with his opponents, he was humble with his poor patients; bitter and savage in his relentless attacks upon his political enemies, he emancipated the insane from their wretched lot, establishing humane conditions of confinement and treatment for them; fighting for his country because he believed in the righteousness of her cause, he embarrassed her perilously by his tenacious attacks upon those policies which he believed wrong. This brilliant, contradictory man has left an indelible impression upon the history of our country, upon the Art and Science of Medicine, and upon the development of principles of honesty and humanity.

Studies in Uncommon Diseases

(*Continued from page* 48)

Catarrhal jaundice is non-contagious and has a different clinical course; acute yellow atrophy never shows an enlarged liver. Specific meningitis must be considered, bearing in mind that the leptospira itself may cause a meningitis. In the early stages, typhoid and paratyphoid must be ruled out (4).

Treatment consists almost wholly of injections of immune antisera prepared in the horse. To be efficient it must be given early; once jaundice has developed, antiserum is ineffective (the use of polyvalent serum is recommended). When serum is given early Tokuyama reports that 20 cc. cause the leptospira to disappear almost completely from the blood in 2-3 hrs (16). Arsenic and antimony compounds are of no help.

In Japan active immunization of man is performed, and has apparently lowered the incidence of the disease (10). Here in the United States it will be interesting to see if the incidence of the disease rises as more attention is given it; there will undoubtedly be a small increase in the number of reported cases, but it remains for time to decide whether a significant enough rise will result to challenge the inclusion of Weil's disease in a series of articles on uncommon diseases.

BIBLIOGRAPHY

1. Jeghers and Houghton, Arch. Path. **20**: 447-476, 1935.
2. Blake, F. G., NEJM, **223**: 561, 1940.
3. Proger, S., Bull. N. E. Med. Center, **2**: 373, 1940.
4. Naegeli, Differential Diagnosis in Internal Medicine, S. B. Debour Co. Chicago, 1940.
5. Glotzer, S., JAMA **110**: 2143-2145, 1938.
6. Haschec and Tobey, JAMA **113**: 1319, 1939.
7. Vagn and Mortensen, Lancet, **238**: 117, 1940.
8. Meakins, Textbook of Medicine, 2nd Ed. Mosby and Co., St. Louis, 1938.
9. Zinsser, H., Textbook of Bacteriology, 7th Ed., Appleton-Century Co., New York, 1928.
10. Stitt, Clough and Clough, Bacteriology, Blakiston, Philadelphia, 1938.
11. Greene-Farrell, Arch. Int. Med., **65**: 847, 1940.
12. JAMA, **113**: 1048, 1939.
13. Cullinan, Proc. Royal Soc. Med., **32**: 933-950, 1939.
14. NYS Jour. Med., **39**: 1969, 1939.
15. Brown and Broom, Brit. Med. Jour., **1**: 1178.
16. Tokuyama, S., JAMA, **114**: 2159, 1940.
17. Norton, JAMA, **113**: 916, 1939.