Dr. Thomson as to the value of internal fixation. Vitallium, while ideal, is nonessential and in some of the smaller institutions is not available. A good screw driver and a first-rate bone drill are essentials and they are two of the rarest things that one can obtain on short notice in a small hospital. The principles promulgated should be carried to physicians through some agencies such as local fracture committees. The aim should be to overcome the indifference which characterizes the first twelve hours of treatment of compound fractures and emphasizes the hazard which creeps in as the result of delay. I should like to ask Dr. Thomson if he has had any untoward effects from postoperative roentgen therapy.

DR. MYRON O. HENRY, Minneapolis: Dr. Thomson deserves congratulations for this valuable paper. I want to emphasize four of his commandments, the four s's surgery, serum, splint and sulfanilamide in compound fractures. The last war taught us the value of débridement, but since the advent of sulfanilamide I believe that débridement need not be so blindly extensive as we formerly did it. It is well to remember too, as Dr. Thomson advised, that débridement should be "conservative and intelligent, with proper respect for anatomic structures." The local implantation of sulfanilamide crystals in compound fractures originated in the Minneapolis General Hospital by house officers Jensen, Johnsrud and Nelson in 1937. Their work was reported in *Surgery* in July 1939. I had the opportunity of following some of this work in its early stages. These men found that the incidence of severe infections in compound fractures was about 25 per cent in the Minneapolis General Hospital cases. Böhler is the only man who has reported a lower incidence and he stated that in Vienna the incidence of "severe" infections was only 8 per cent. They must have fewer staphylococci in Vienna. By local implantation of sulfanilamide crystals this incidence in the Minneapolis series has been lowered to less than 5 per cent. The amount of sulfanilamide used depends on the extent of the trauma and the extent of the contamination; 20 Gm. is the average limit for adults and from 5 to 15 Gm. is sufficient for average to severe wounds. The drug apparently does act locally and it seems to be more efficient by local implantation than by oral administration in these cases. It may delay wound healing slightly but its absorption from the tissues is slow, and this gives a prolonged sulfanilamide effect. As much as 40 Gm. can be given in severe cases. I think it is wise to remember, though, that sulfanilamide is not bactericidal for staphylococci but only bacteriostatic.

DR. HAROLD R. BOHLMAN, Baltimore: I wish to emphasize three points: First, avoid tension in all compound fractures and traumatic wounds. If capillary circulation is obliterated, serum and white blood cells are impotent. Clostridia, injured tissues and impaired circulation are sure to cause gas gangrene. I have sections of such tissues in which Clostridia have grown so rapidly that no cellular reaction whatever is present. Second, instead of closing so many wounds, one should leave them open more frequently and often enough, particularly in gunshot wounds, counter incisions should be made, relieving tension in all fascial compartments. These wounds should be thoroughly washed and freed of foreign material. In July 1937 I published the first article on treatment of gas gangrene with sulfanilamide. The prophecies in this article have been well borne out by subsequent experience. I administered sulfanilamide by mouth and introduced crystals directly into wounds but thought that oral administration produced the results so discontinued local use, resuming it again after Jensen and co-workers published their report. It delays healing and is toxic for some individuals. It is tremendously bacteriostatic for all ordinary organisms in the high local concentrations thus attained. It greatly reduces the incidence of wound infections but may produce more scar tissue. A word of caution regarding sulfanilamide: Adequate dosage and control are necessary. There is no way of prophesying how it will affect an individual. A daily red blood cell and white blood cell count and blood concentration level determination are necessary. Débridement is entirely unnecessary in many wounds when proper sulfanilamide therapy is employed. I mention the following not as suggested treatment but to emphasize this point: In six cases I have used no sterilizing compounds on or in the wounds, simply covering them with petrolatum gauze and rapidly raising the blood level of sulfanilamide 10 mg. per hundred cubic centimeters. Some were extensively macerated wounds of the tibia and ankle, but healing occurred with scarcely any scar resulting; no infections occurred. I have seen some severe reactions when roentgen therapy was combined with sulfanilamide. Bear in mind that some people do not tolerate sun on their skins while taking this drug. X-rays seem to have some similar effect. I can see no reasons for subjecting a badly injured patient to the ordeal of extensive moving for roentgen therapy.

DR. JAMES E. M. THOMSON, Lincoln, Neb.: With regard to roentgen therapy, it is true that a few reactions occurred, but nothing of a serious nature locally. Unlike the method that Dr. Bohlman suggests, I use the mobile unit and send it up to the room and have the patient treated there. It isn't a heavy dose of x-rays: it is only 30 or 40 roentgens, and it is a very simple matter to do that with a portable unit. Another thing about sulfanilamide and its use: In cases that are going to surgery, in which there has previously been an infective process, and although apparently clean, there is the potential possibility of lighting up an old infection. I have felt that the prophylactic use of sulfanilamide had a direct influence in preventing the awakening of infection. There were in this group forty-nine cases with fifty-three fractures, and unfortunately I couldn't show the statistical slides. Thirty-five had good results, and I mean by that that there was less than 10 per cent partial or permanent disability in the leg or arm for the profession or work that they were in. Twelve had fair results. There was no gas gangrene. There were two amputations. One was an amputation because of extensive laceration, and the second was one in which a mistake in judgment on my part led to an amputation due to circulatory insufficiency a year and a half after the fracture.

TREATMENT OF ADDISON'S DISEASE WITH DESOXYCORTICOSTERONE ACETATE

BY INTRAMUSCULAR INJECTIONS AND SUBCUTANEOUS IMPLANTATION OF PELLETS

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Within the past twelve years there has occurred a tremendous increase both in the understanding of the pathologic physiology and in the treatment of Addison's disease. The study of this particular problem received its impetus essentially as a result of two major contributions, the preparation of a fairly potent adrenal cortex extract [1] and the recognition of the underlying blood electrolyte disturbances which occurred in the presence of destruction of the adrenal cortex.[2]

From the Medical Services of Drs. George Baehr and B. S. Oppenheimer, Mount Sinai Hospital.
The implantation of pellets was performed by Dr. John H. Garlock, attending surgeon, Mount Sinai Hospital.
The desoxycorticosterone acetate for intramuscular injections was given to us by Ciba Pharmaceutical Products, Inc., Summit, N. J.
The pellets of desoxycorticosterone acetate were supplied to us by Dr. George W. Thorn of the Johns Hopkins Hospital, Baltimore.

1. Hartman, F. A.; MacArthur, C. G.; and Hartman, W. E.: A Substance Which Prolongs the Life of Adrenalectomized Cats, Proc. Soc. Exper. Biol. & Med. **25**: 69 (Oct.) 1927. Rogoff, J. M., and Stewart, G. N.: The Influence of Adrenal Extracts on the Survival Period of Adrenalectomized Animals, Science **66**: 327 (Oct.) 1927. Pfiffner, J. J., and Swingle, W. W.: The Preparation of an Active Extract of the Suprarenal Cortex, Anat. Rec. **44**: 225 (Dec.) 1929.

2. Loeb, R. F.: Chemical Changes in the Blood in Addison's Disease, Science **76**: 420 (Nov. 4) 1932. Loeb, R. F.; Atchley, D. W.; Benedict, Ethel M., and Leland, Jessica: Electrolyte Balance Studies in Adrenalectomized Dogs, with Particular Reference to the Excretion of Sodium, J. Exper. Med. **57**: 775 (May) 1933. Harrop, G. A.; Weinstein, Albert; Soffer, L. J., and Trescher, J. H.: The Diagnosis and Treatme t of Addison's Disease, J. A. M. A. **100**: 1850 (June 10) 1933. Harrop, G. A.; Soffer, L. J.; Ellsworth, Read, and Trescher, J. H.: Plasma Electrolytes and Electrolyte Excretion During Suprarenal Insufficiency in the Dog, J. Exper. Med. **58**: 17 (July) 1933.

The results of these investigations showed that destruction of the adrenal cortex was followed by a marked excretion of sodium and chloride in the urine, a pronounced drop in the blood concentration of these ions, an increase in the blood potassium, and hemoconcentration and nitrogen retention. Treatment was directed toward reestablishment of a normal blood electrolyte pattern. This was accomplished both with the aid of injections of cortical extract and with the addition of large quantities of salt (from 10 to 20 Gm.) to the diet. Wilder and his co-workers [3] pointed out the importance and need for the restriction of the potassium intake in the diet.

Although this represented an improvement in the treatment of Addison's disease, it still left much to be desired. The adrenal cortex extract was available in limited quantities and was of limited potency. The large quantities of salt which patients had to consume were irksome to them, and the improvement in the general condition of these patients was not unduly striking. It was evident that further advancement in the treatment of this disease was dependent on the preparation of a more potent extract which could preferably be prepared synthetically.

In 1936 and 1937 Mason, Myers and Kendall [4] and de Fremery and his co-workers [5] isolated corticosterone and dehydrocorticosterone in crystalline form from the extracts of the adrenal cortex and found that they could maintain adrenalectomized animals in good condition. A short while later, Steiger and Reichstein [6] announced the preparation of desoxycorticosterone acetate from stigmasterol, and subsequently Reichstein and von Euw [7] succeeded in recovering this compound from an extract of the adrenal cortex. Levy-Simpson [8] used desoxycorticosterone acetate in the treatment of two patients with Addison's disease and found that it exercised an effect qualitatively similar to that of adrenal cortex extract.

In 1938 Thorn and his co-workers [9] used desoxycorticosterone acetate in the treatment of bilaterally adrenalectomized dogs. They found that it was effective in maintaining these animals in good condition despite a diet low in sodium and chloride. Withdrawal of the drug resulted in a prompt diuresis with loss of sodium and chloride ions in the urine, a decrease in urinary potassium, hemoconcentration and elevation of blood nonprotein nitrogen, and the development of symptoms of adrenal insufficiency. Thorn, Howard and Emerson [10] subsequently used this compound in the treatment of eight patients with Addison's disease. They found that treatment in doses of from 2 to 30 mg. daily resulted in a marked improvement in the clinical condition of the patient, as well as the restoration of the blood electrolyte pattern to normal. These changes occurred without supplementary treatment with sodium salts or a decrease in the potassium content of the diet. The authors felt that results of treatment with desoxycorticosterone acetate resembled in every way the effect obtained with a potent cortical extract. Ferrebee, Ragan, Atchley and Loeb [11] treated thirteen patients with Addison's disease with intramuscular desoxycorticosterone acetate and propionate. They found that improvement was greater than from any previous therapy. Their results were in general agreement with those reported by Thorn and his group.[10] In three of their patients, however, definite hypertension developed during the course of treatment, and ten of their patients had edema, which varied from mild puffiness of the face and ankles to massive anasarca. Of this group of ten, cardiac insufficiency developed in three.

In 1937 Deanesly and Parkes [12] reported that the subcutaneous implantation of pellets of estrogens and androgens produced a prolongation of the hormonal effect. Ingle and Mason [13] succeeded in prolonging the survival period of adrenalectomized rats by implanting subcutaneously tablets composed of a mixture of cholesterol and compounds derived from the adrenal cortex. Thorn and his co-workers,[14] utilizing the technic employed by Deanesly and Parkes, studied the effect of subcutaneously implanted pellets of desoxycorticosterone acetate in bilaterally adrenalectomized dogs and six patients with Addison's disease. They find that results obtained with the pellets are similar to those with intramuscular injections except that the former effect a greater economy in the use of the drug. They conclude that the life of a pellet depends on its consistency and weight. The quantity of desoxycorticosterone acetate liberated appears to vary with the surface area of the pellet. The pellets are absorbed at the rate of 0.25 to 0.40 mg. daily.

RESULTS

In the present paper we present the results obtained in five patients with Addison's disease, who were treated with intramuscular injections of desoxycorticosterone acetate in oil. Four of these patients subsequently received pellets of the synthetic crystalline compound implanted subcutaneously. One of the patients was a female and four were males. Their ages varied between 11 and 44 years. All the patients had been previously treated with large amounts of salt by mouth, and four of them at some time or other received injections of adrenal cortex extract:

CASE 1.—D. G., a woman aged 21, was admitted to the hospital March 21, 1938, because of marked asthenia, pigmentation, nausea and loss of 20 pounds (9 Kg.) in weight. The blood pressure could not be determined by auscultation, but by palpation the systolic pressure was found to be 70. The blood urea nitrogen was 17 mg. per hundred cubic centimeters,

3. Wilder, R. M.; Snell, A. M.; Kepler, E. J.; Rynearson, E. H.; Adams, Mildred, and Kendall, E. C.: Control of Addison's Disease with a Diet Restricted in Potassium: A Clinical Study, Proc. Staff Meet., Mayo Clin. **11**: 273 (April 29) 1936.

4. Mason, H. L.; Myers, C. S., and Kendall, E. C.: Chemical Studies of the Suprarenal Cortex, J. Biol. Chem. **116**: 267 (Nov.) 1936.

5. de Fremery, P.; Laqueur, E.; Reichstein, T.; Spanhoff, R. W., and Uyldert, I. E.: Corticosterone, a Crystallized Compound with the Biological Activity of the Adrenal-Cortical Hormone, Nature, London **139**: 26 (Jan. 2) 1937.

6. Steiger, Marguerite and Reichstein, T.: Desoxy-Corticosterone (21-Oxy-Progesteron aus Δ^5-3-Oxy-ätio Cholensäure), Helvet. Chim. acta **20**: 1164, 1937.

7. Reichstein, T., and von Euw, J.: Ueber Bestandteile der Nebennierenrinde: Isolierung der Substanzen Q (Desoxy-Corticosteron) und R sowie wieterer Stoffe, Helvet. chim. acta **21**: 1197, 1938.

8. Levy-Simpson, Samuel: The Use of Synthetic Desoxycorticosterone Acetate in Addison's Disease, Lancet **2**: 557 (Sept. 3) 1938.

9. Thorn, G. W.; Engel, L. L., and Eisenberg, Harry: The Effect of Corticosterone and Related Compounds on the Renal Excretion of Electrolytes, J. Exper. Med. **68**: 161 (Aug.) 1938; Studies on Desoxycorticosterone, a Synthetic Adrenal Cortical Hormone, Endocrinology **25**: 39 (July) 1939.

10. Thorn, G. W.; Howard, R. P., and Emerson, Kendall, Jr.: Treatment of Addison's Disease with Desoxycorticosterone Acetate, a Synthetic Adrenal Cortical Hormone, J. Clin. Investigation **18**: 449 (July) 1939.

11. Ferrebee, J. W.; Ragan, Charles; Atchley, D. W., and Loeb, R. F.: Desoxycorticosterone Esters: Certain Effects in the Treatment of Addison's Disease, J. A. M. A. **113**: 1725 (Nov. 4) 1939.

12. Deanesly, R., and Parkes, A. S.: Factors Influencing the Effectiveness of Administered Hormones, Proc. Roy. Soc., London, s. B **124**: 279 (Dec. 7) 1937; Further Experiments on the Administration of Hormones by the Subcutaneous Implantation of Tablets, Lancet **2**: 606 (Sept. 10) 1938.

13. Ingle, D. J., and Mason, A. L.: Subcutaneous Administration of Cortin Compounds in Solid Form to the Rat, Proc. Soc. Exper. Biol. & Med. **39**: 154 (Oct.) 1938.

14. Thorn, G. W.; Engel, L. L., and Eisenberg, H.: Treatment of Adrenal Insufficiency by Means of Subcutaneous Implants of Pellets of Desoxycorticosterone Acetate (a Synthetic Adrenal Cortical Hormone), Bull. Johns Hopkins Hosp. **64**: 155 (March) 1939. Thorn, G. W.; Howard, R. P.; Emerson, Kendall, Jr., and Firor, W. M.: Treatment of Addison's Disease with Pellets of Crystalline Adrenal Cortical Hormone Implanted Subcutaneously, ibid. **64**: 339 (May) 1939.

blood chlorides 93 milliequivalents per liter, sodium 131.3 milliequivalents per liter and sugar 79 mg. per hundred cubic centimeters. She was treated with a constant intravenous drip of isotonic saline solution and during the ensuing twenty-four hours received approximately 3,000 cc. As a result of the intravenous therapy she improved sufficiently to continue oral treatment with salt. During the course of the next week she was given 9 Gm. of sodium chloride and 4 Gm. of sodium bicarbonate daily by mouth. Her blood pressure rose to 95 systolic, 60 diastolic; the weight was 113 pounds (51 Kg.). The blood chemistry values had now altered, so that the sodium was 138.3, chlorides 100.0 and potassium 6.3 milliequivalents per liter. The blood sugar rose to 100 mg. per hundred cubic centimeters; the urea nitrogen, however, remained stationary at 16 mg. From June 16 to 19, approximately three months after oral treatment with salt had been started, the patient without our knowledge omitted her daily supplementary

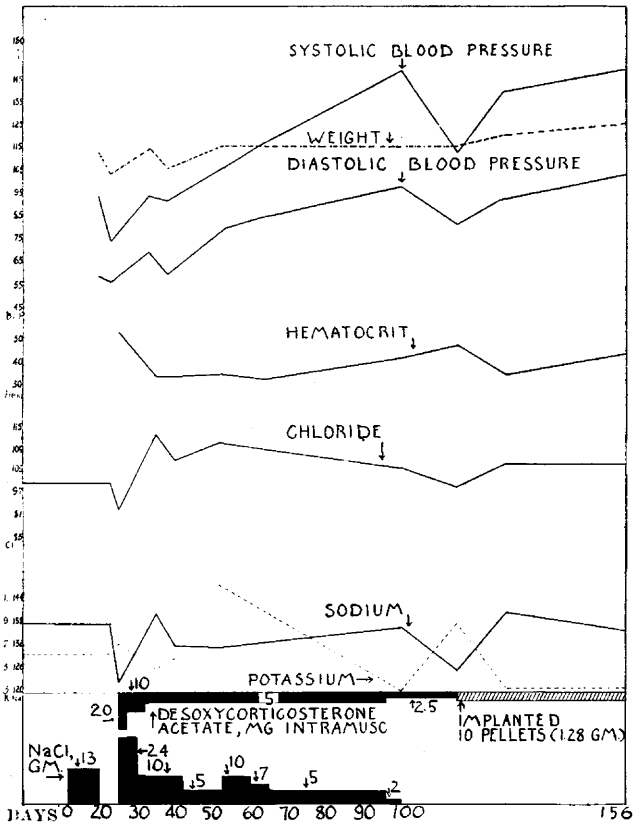

Chart 1.—Course in case 1.

salt feedings and was promptly precipitated into addisonian crisis. The blood pressure fell to 75 systolic, 58 diastolic. The blood values were sodium 122.3, chlorides 93.5 and potassium 7.2 milliequivalents per liter. The urea nitrogen was 34 and sugar 90 mg. per hundred cubic centimeters. The carbon dioxide content was 22.6 millimols per liter. The volume of packed red cells was 54 per cent, and the body weight had fallen to 104 pounds (47 Kg.).

During the three months period in which the patient was treated with salt alone, we find that the blood electrolytes were maintained at a fairly normal level. However, at no time did she feel well. She continued to complain of profound asthenia and anorexia and could spend but little time out of bed. June 19, when the symptoms of crisis developed, intramuscular injections of desoxycorticosterone acetate were started. She received 20 mg. of the synthetic substance daily for two days, then 10 mg. daily for four days. In addition, during this six day period she received 16 Gm. of salt by mouth daily. At the end of this period her weight had risen to 116 pounds (53 Kg.), the blood pressure was 90 systolic, 65 diastolic and the hematocrit reading had fallen to 35 per cent. The blood values now were sodium 139.9, chlorides 113.5 and potassium 5.1 milliequivalents per liter; the urea nitrogen was 12 mg. per hundred cubic centimeters and the carbon dioxide content was 23.0 millimols per liter. From June 24 until July 15 the patient received 10 Gm. of supplementary salt by mouth and 5 mg. of desoxycorticosterone acetate intramuscularly daily, but from July until the end of the first week in September the daily supplementary salt intake was reduced to 5 Gm. At the end of this period the patient's clinical condition improved remarkably. She was up and out of bed, she had a sense of well-being, her appetite had improved, and the pigmentation had decreased somewhat. The blood pressure was now 150 systolic, 94 diastolic; the weight was 117 pounds (53 Kg.). The blood electrolyte studies showed the sodium to be 137.8 milliequivalents, chlorides 107.0 milliequivalents and potassium 3.6 milliequivalents per liter, urea nitrogen 10 mg. and sugar 90 mg. per hundred cubic centimeters, carbon dioxide 24.8 millimols per liter, and the blood hematocrit value 43 per cent. Because of the hypertension, the supplementary salt feedings were entirely discontinued, and the desoxycorticosterone acetate was reduced to 2.5 mg., given intramuscularly daily. After one week of this regimen the blood pressure fell to 112 systolic, 78 diastolic; the blood sodium was 127, chlorides 102 and potassium 9.2 milliequivalents per liter. It was obvious that 2.5 mg. of the drug given intramuscularly daily without additional salt was inadequate to maintain a normal electrolyte pattern. Despite the abnormalities of the blood constituents, however, her sense of well-being continued, and the patient was up and about without any discomfort.

September 16 ten pellets of crystalline desoxycorticosterone acetate were implanted subcutaneously, the average weight of each pellet being 128 mg. It was calculated that approximately 0.3 mg. of the compound would be absorbed daily per pellet, the total daily amount being 3 mg. This is equivalent in therapeutic effect to about 5 mg. given intramuscularly. She received no supplementary salt by mouth. One week after the implantation of the pellets her weight was 120 pounds (54 Kg.), the blood pressure was 138 systolic, 92 diastolic, and the hematocrit level had fallen to 34 per cent. The blood values now were sodium 141.8, chlorides 107.5 and potassium 3.6 milliequivalents per liter. She felt perfectly well and was discharged from the hospital. November 10, two months after implantation of the pellets, the blood pressure had risen to 150 systolic, 95 diastolic, and on slight exertion it would rise to 180 systolic, 110 diastolic, which was associated with dyspnea and cardiac palpitation. Her weight was 122 pounds (55 Kg.), and the blood electrolytes were entirely normal.

During the period of treatment with desoxycorticosterone acetate there occurred a tremendous improvement as far as the symptoms related to the Addison's disease were concerned, despite the fact that no additional salt was required. However, the symptoms of mild cardiac failure were a cause for considerable concern; they were probably due to the liberation of excessive amounts of the desoxycorticosterone acetate. She is to be readmitted to the hospital for the removal of some of the implanted pellets.

CASE 2.—S. R., a man aged 19, was admitted to the hospital Nov. 25, 1938, with all the characteristic signs and symptoms of Addison's disease. On admission, the hemoglobin was 101 per cent and the red blood cell count was 7,500,000, showing considerable hemoconcentration. The blood sodium was 128.3, chlorides 85 and potassium 8.1 milliequivalents per liter. The blood urea nitrogen was 27 mg. and the sugar 100 mg. per hundred cubic centimeters. His weight was 113 pounds (51 Kg.) and blood pressure 90 systolic, 50 diastolic. The patient was given 12 Gm. of sodium chloride and 4 Gm. of sodium bicarbonate daily by mouth. In addition, during the first two weeks he received 2 cc. of adrenal cortex extract subcutaneously daily. After seven weeks of treatment with salt alone he was discharged from the hospital considerably improved, although he continued to complain of weakness and some anorexia. His blood pressure on discharge had risen to 112 systolic, 70 diastolic, and the blood sodium had increased to 135 milliequivalents per liter.

He was readmitted to the hospital May 19, 1939. During the intervening six months period he had been taking daily 12 Gm. of salt and 4 Gm. of sodium bicarbonate. His weight had increased to 133 pounds (60 Kg.), and the blood pressure was 110 systolic, 80 diastolic. The blood chemical values now were sodium 133.1, chlorides 100 and potassium 9.6 milliequivalents per liter, urea nitrogen 15 and sugar 90 mg. per hundred cubic centimeters, and carbon dioxide content 25.5 millimols per liter. During this period of supplementary salt treatment he continued to feel weak, had one or two daily episodes of nausea and was entirely incapable of doing any work.

One week after his readmission to the hospital, treatment was begun with desoxycorticosterone acetate. He received a daily intramuscular injection of 5 mg. of the drug in oil, and the supplementary sodium chloride intake was reduced to 10 Gm. After one week of this treatment, the blood electrolytes returned to normal levels, the sodium increasing to 137.8 and chlorides to 105 milliequivalents per liter. His weight increased to 138 pounds (63 Kg.), but the blood pressure stayed relatively stationary at 105 systolic, 65 diastolic. Despite the improvement in blood chemistry values there occurred no change in symptoms. He continued to complain of weakness and occasional episodes of nausea. Three weeks after the intramuscular injections were started, ten pellets of crystalline desoxycorticosterone acetate were implanted subcutaneously in the right infrascapular region. The average weight of each pellet was 103 mg. For two days after the implantation of the pellets he continued to receive the supplementary 10 Gm. of salt by mouth. At the end of this period he began to complain of headache, vomiting, edema of the face and hands, palpitation and exertional dyspnea. It was noted that a gallop rhythm had developed. His weight at this time was 138 pounds and the blood pressure had risen to between 130 systolic, 85 diastolic, and 136 systolic, 102 diastolic. The blood electrolytes, however, showed no material change from the previous levels. The sodium was 137.7, chlorides 108.5, and potassium 7.1 milliequivalents per liter. The urea nitrogen was 10 and the sugar 80 mg. per hundred cubic centimeters, while the carbon dioxide content was 23.9 millimols per liter. The daily salt intake was promptly reduced and the headache, vomiting, and edema disappeared. On discharge from the hospital July 18, 1939, one month after implantation of the pellets, he was taking only 2 Gm. of additional salt by mouth, his weight was 139 pounds (63 Kg.) and the blood pressure 124 systolic, 80 diastolic. The blood electrolytes were entirely normal. Symptomatically there occurred a marked improvement. He felt quite strong and was anxious to return to work. Anorexia and nausea had entirely disappeared. He has been followed regularly with repeated blood chemistry determinations. In October 1939 the additional salt by mouth was entirely discontinued. In December 1939, six months after implantation of the pellets, the patient continues to feel extraordinarily well. His blood pressure, however, has risen to 140 systolic, 90 diastolic. The blood electrolyte pattern continues to remain normal.

This patient, like the one previously described, could get along only poorly when treated with large amounts of salt alone. Even after administration of a potent adrenal cortex extract there was but little change in the clinical condition, although the blood chemical constituents were approximately normal. Following the administration of the desoxycorticosterone acetate, however, there occurred marked improvement in symptoms, the most striking of which was the tremendous increase in the sense of well-being. There were improvement in strength and appetite and a complete disappearance of the gastrointestinal symptoms. However, on implantation of pellets there developed hypertension and edema and some signs of heart failure, although relatively mild in degree.

CASE 3.—J. S., a man aged 44, was admitted to the hospital May 24, 1939, because of pigmentation, progressive asthenia and fatigue, anorexia, nausea, and loss of 16 pounds (7 Kg.) in weight in two weeks. His blood pressure on admission was 100 systolic, 75 diastolic and he weighed 118 pounds (53.5 Kg.). He presented a characteristic picture of Addison's disease in mild crisis. The blood chemical values were sodium 127.6 and chlorides 94.0 milliequivalents per liter, urea nitrogen 19 mg. and sugar 105 mg. per hundred cubic centimeters. Treatment was begun with 15 Gm. of salt by mouth daily in addition to the salt content of the usual ward diet. At the end of one month of this regimen, his weight was still 118 pounds and the blood pressure 105 systolic, 65 diastolic. The blood sodium rose only slightly to 130.5 and chlorides to 97 milliequivalents per liter while the potassium was 7.4 milliequivalents. The blood urea nitrogen was 14 mg., and the volume of packed red blood cells was 41.5 per cent. There was no improvement in the clinical condition. He continued to complain of profound weakness, anorexia and nausea. June 29, in addition to treatment with 15 Gm. of salt, intramuscular injection of 5 mg. of desoxycorticosterone acetate daily were started. After eleven days of the combined therapy his weight increased to 125 pounds (57 Kg.), the blood pressure rose to 125 systolic, 80 diastolic,

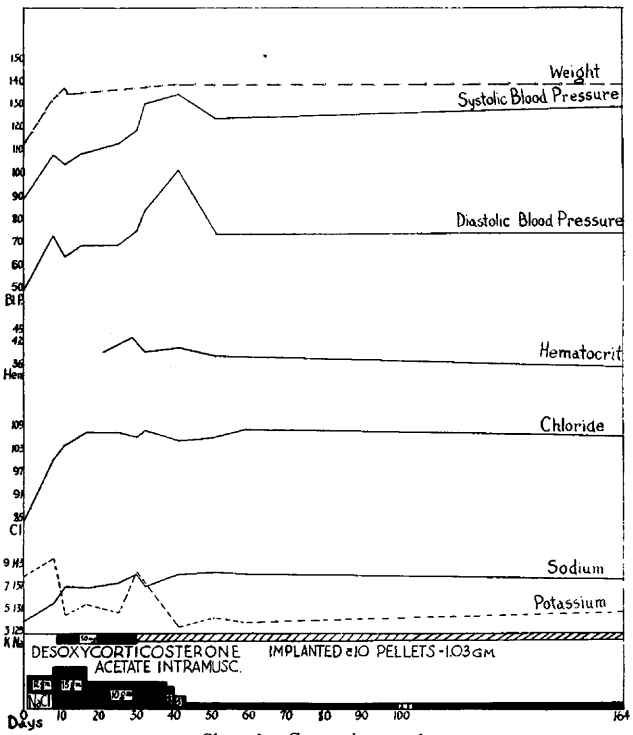

Chart 2.—Course in case 2.

and the hematocrit value dropped to 28 per cent. The blood electrolytes now were perfectly normal. The blood sodium was 138.3, chlorides 105.5 and potassium 4.5 milliequivalents per liter, while the urea nitrogen was 13 and the sugar 90 mg. per hundred cubic centimeters. The carbon dioxide content of the blood was 29 millimols per liter. Although there occurred this marked improvement in the laboratory observations, clinical improvement was not so striking. The anorexia and nausea had subsided considerably but the patient continued to complain of weakness. The supplementary sodium chloride intake was reduced to 10 Gm. daily, and seventeen days later thirteen pellets of the crystalline desoxycorticosterone acetate were implanted subcutaneously in the left infrascapular region. The average weight of each pellet was 126 mg. It was calculated that the daily absorption of the drug from the pellets would total 3.9 mg. Six weeks after implantation of the pellets the symptoms of Addison's disease had improved considerably. Anorexia and nausea had vanished, and the patient felt considerably stronger. However, he now began to complain of precordial pain on exertion, dyspnea and cardiac palpitation. The precordial pain was somewhat relieved by glyceryl trinitrate. The blood pressure at this time was 140 systolic, 85 diastolic, the hematocrit value was 33.5 per cent and blood

sodium 139, chlorides 105 and potassium 5.9 milliequivalents per liter. The supplementary salt by mouth was entirely discontinued but the precordial discomfort continued and the patient was now seriously handicapped by his cardiac symptoms. Two months after implantation of the pellets the blood electrolytes continued to be normal but the blood pressure varied from 150 systolic, 80 diastolic to 184 systolic, 98 diastolic. It was decided to remove some of the implanted pellets, and September 26 four pellets were removed surgically.

The blood pressure promptly fell to 140 systolic, 85 diastolic and the attacks of palpitation and precordial pain were somewhat less frequent. At present, one month after removal of the four pellets, the blood pressure continues at 145 systolic, 88 diastolic, his weight is 121 pounds (55 Kg.) and the blood sodium is 137.5, chlorides 102.5 and potassium 3.6 milliequivalents per liter. The blood urea nitrogen is 7.0 and the sugar is 80 mg. per hundred cubic centimeters. The patient has had no additional salt during this period. However, the anginal symptoms persist, although with somewhat lessened intensity.

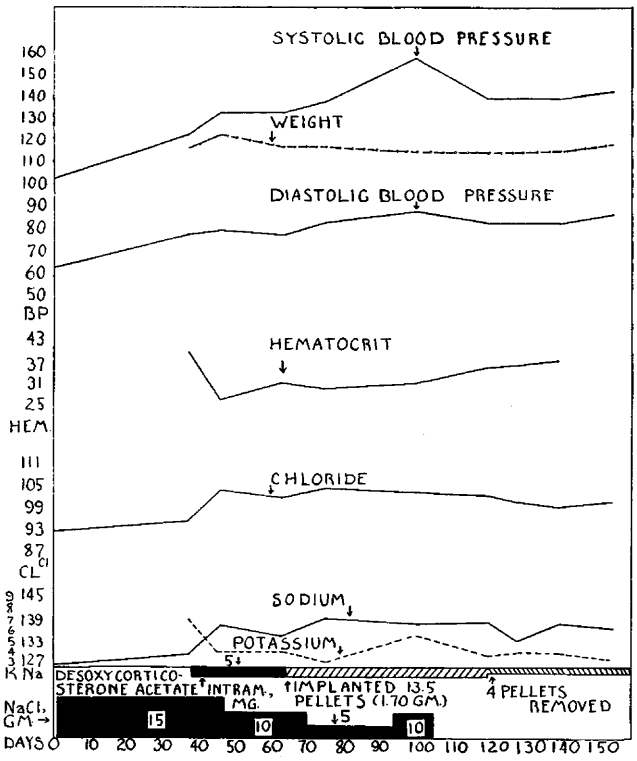

Chart 3.—Course in case 3.

We feel that it will be necessary to remove more pellets, despite the fact that the amount of the drug being absorbed is only approximately 2.7 mg. daily.

This patient represents the third of this series, all of whom have behaved in essentially the same fashion. After treatment with desoxycorticosterone acetate they progressed remarkably well from the point of view of Addison's disease. This subjective and objective improvement continued without the necessity for taking additional salt by mouth. However, in all three patients hypertension has developed, and in two of them it was severe enough to warrant removal of some of the implanted pellets.

Case 4.—L. C., a man aged 34, was admitted to the hospital Nov. 20, 1939, after being treated elsewhere for Addison's disease. For a month prior to admission to the hospital he had received 16 Gm. of salt by mouth daily, plus injections of 5 cc. of adrenal cortex extract twice a week. On admission to the hospital his weight was 129 pounds (58.5 Kg.), blood pressure 94 systolic, 66 diastolic and hematocrit value 47 per cent. The blood sodium was 127 and chlorides 100 milliequivalents per liter. The blood urea nitrogen was 21 and sugar 95 mg. per hundred cubic centimeters. The carbon dioxide content was 26.5 millimols per liter. From November 20 until November 30 he was treated with 15 Gm. of salt by mouth without any additional extract. At the end of this period of time, he had lost 2 pounds (0.9 Kg.) in weight but there was no change in the blood electrolytes, blood pressure or hematocrit reading. He continued to complain of nausea and profound asthenia, and the intensity of pigmentation increased. November 30, daily intramuscular injections of 5 mg. of desoxycorticosterone were started in addition to the 15 Gm. of salt. There occurred an immediate improvement in clinical symptoms and by December 11 he felt well enough to get out of bed; nausea and anorexia had entirely disappeared and he felt considerably stronger. His weight at this time had increased to 132½ pounds (60 Kg.), blood pressure was 102 systolic, 68 diastolic and the hematocrit level had fallen to 39 per cent. The blood electrolyte pattern returned to normal, the blood sodium being 140.6 and chlorides 107 milliequivalents per liter; blood urea nitrogen was 6 mg. and sugar 60 mg. per hundred cubic centimeters, while the carbon dioxide content was 28.1 millimols per liter. December 19 the injected dose of desoxycorticosterone acetate was reduced to 2.5 mg. daily while the supplementary salt feeding had been decreased to 5.0 Gm. daily. Eight days later with this regimen his weight had increased to 136½ pounds (62 Kg.); the blood pressure and hematocrit level remained constant at 106 systolic, 64 diastolic and 38 per cent respectively. The blood sodium was 143.9 and chlorides 109 milliequivalents per liter, urea nitrogen 12 mg. and sugar 75 mg. per hundred cubic centimeters, and the carbon dioxide content was 25.8 millimols per liter. The desoxycorticosterone acetate was now reduced to 1.5 mg. with 5 Gm. of salt daily. Six days later there was no change in the weight or blood pressure, and the blood chemical constituents remained perfectly normal. Clinically the patient felt very well. Jan. 6, 1940, three pellets of crystalline desoxycorticosterone acetate were implanted subcutaneously in the left infrascapular region. The average weight of each pellet was 110 mg. and it was calculated that he would absorb approximately 0.9 mg. of the drug daily. In addition he receives 5 Gm. of salt by mouth. At present, two weeks after the implantation of the pellets, he continues to feel perfectly well and is anxious to go back to work. There has been no further change in his blood pressure, and the blood electrolytes remain normal.

In this case we attempted to avoid the development of the complications in other cases following the use of the synthetic compound. In previous cases the therapeutic goal desired was the ultimate treatment with desoxycorticosterone acetate without the supplementary daily salt feedings. This required the use of rather large amounts of desoxycorticosterone, and consequently there developed hypertension, edema or both. In this last case the amount of the substance decided on was less than the amount that would be required if no additional salt was to be used. To date this patient has had none of the sequelae seen in our patients treated with the large doses of desoxycorticosterone acetate. With the aid of a small amount of salt (5 Gm.) daily in addition to his regular diet he is doing extremely well.

Case 5.—This case will be reported in greater detail elsewhere by the department of pediatrics of the hospital. Briefly, S. S., a boy aged 11, was admitted to the hospital April 15, 1938, in severe addisonian crisis, with a well defined history of Addison's disease of at least six months' duration. On admission his weight was 72 pounds (33 Kg.), blood pressure 64 systolic, 42 diastolic, blood urea nitrogen 51 mg. per hundred cubic centimeters, and blood sodium 114.7 and chlorides 85 milliequivalents per liter. He was given large quantities of intravenous saline solution and dextrose, and April 25 the blood pressure was still 66 systolic, 42 diastolic, blood urea nitrogen 26 mg. and sugar 100 mg. The blood electrolytes were sodium 120.5, chlorides 85 and potassium 6.9 milliequivalents per liter.

Clinically he was somewhat improved, although he continued to be listless and rather drowsy.

He was started on 10 Gm. of salt and 5 Gm. of sodium bicarbonate daily by mouth. Under this regimen he became more alert and seemed somewhat stronger. June 10, six weeks after oral salt therapy was begun, he was still seriously ill.

TABLE 1.—*Dextrose Tolerance Curves* in Patients with Addison's Disease Before and After Treatment with Desoxycorticosterone Acetate Blood Sugar, Mg./100 Cc.*

Patient and Type of Therapy	Control	½ Hour	1 Hour	2 Hours	3 Hours
1. D. K.					
Treatment with salt alone	55	85	125	110	95
Treatment with desoxycorticosterone acetate, 5 mg. intramuscularly for 68 days	75	125	105	90	85
2 months after pellets were implanted	70	135	115	120	120
2. S. R.					
Treatment with salt alone	85	90	85	85	70
Treatment with desoxycorticosterone acetate for 4 months (injections and pellets)	60	85	75	60	40
4. L. C.					
Treatment with salt alone	50	130	80	85	90
Treatment with desoxycorticosterone acetate for 3 weeks (injections)	90	105	100	85	80
5. S. S.					
Treatment with salt alone	60	115	80	90	90
Treatment with desoxycorticosterone acetate for 2 months (injections)	80	105	80	95	75

* 1.75 Gm. of dextrose per kilogram of body weight was administered to the fasting patient.

The blood urea nitrogen was 26 mg. and sugar 50 mg. per hundred cubic centimeters, while the blood sodium was 125.2 and chlorides 105 milliequivalents per liter, although the blood pressure had gone up to 96 systolic, 56 diastolic. At this point he began to receive 2 cc. of adrenal cortex extract subcutaneously in addition to the salt. Four months later (October 6) his weight had increased to 79 pounds (36 Kg.), the blood pressure was 100 systolic, 60 diastolic and the blood electrolytes were entirely normal. He was discharged from the hospital and during the course of the next year he received 15 Gm. of salt by mouth and 2 cc. of adrenal cortex extract subcutaneously twice a week. One year after discharge from the hospital, Oct. 4, 1939, he had gained 18 pounds (8 Kg.) in weight and felt fairly well; his blood pressure was 100 systolic, 70 diastolic, blood urea nitrogen 19 mg. and sugar 90 mg. per hundred cubic centimeters. The blood sodium was 139, chlorides 106.5 and potassium 3.6 milliequivalents per liter. The hematocrit value was 40 per cent. He was taken off salt and extract for about forty-eight hours; at the end of this period he began to complain of weakness, nausea and abdominal cramps. There was no change in blood pressure, but the hematocrit value increased to 43 per cent. The blood urea nitrogen had risen to 24 mg. The blood sodium had fallen to 135 and the chlorides to 101.5 milliequivalents per liter, while the potassium increased to 5.4 milliequivalents. October 10 treatment was begun with desoxycorticosterone acetate; during the course of the next month the daily dose was reduced to 1.5 mg., while he received 5 Gm. of additional salt by mouth. The patient felt well, the blood pressure was 104 systolic, 70 diastolic and the weight 99 pounds (45 Kg.), and the blood electrolytes were entirely normal. At this point it was decided to discontinue the desoxycorticosterone acetate entirely but to increase the daily supplementary salt intake again to 15 Gm. Two weeks later, although the blood chemistry values were still perfectly normal, he began to complain of some weakness and his appetite was reduced. His sense of well-being was not as marked as during the period of treatment with the desoxycorticosterone acetate.

COMMENT

The treatment of Addison's disease with desoxycorticosterone acetate represents a marked advance in therapy. It produces not only dramatic changes in the blood chemistry but equally striking changes in the well-being of the patient. The effect of the synthetic compound on the blood electrolytes is qualitatively the same as that with adrenal cortex extract except that the effect of the synthetic substance is more pronounced. With adequate doses of the desoxycorticosterone acetate there occur a retention of blood sodium and chloride and a potassium diuresis. With the reestablishment of a normal blood electrolyte pattern, evidences of dehydration and hemoconcentration disappear and the urea nitrogen returns to normal. In contrast to the effect of the synthetic drug on the blood electrolytes, no effect is produced on carbohydrate metabolism. In four cases (table 1) dextrose tolerance tests were done before and after treatment. There was no demonstrable change in carbohydrate metabolism as a result of the treatment. The tests were performed from three weeks to four months after therapy with the synthetic compound was started.

The effect of the desoxycorticosterone acetate on the blood pressure is apparently dependent on dosage. When the amount of the drug used is in excess of the daily requirement of the patient there will occur an increase in blood pressure which may even reach alarming levels. Thus three of our patients developed a definite hypertension, and one of this group manifested anginal symptoms which incapacitated him almost as completely as did the original uncontrolled Addison's disease. When the dosage is reduced the blood pressure will fall. Although the effect of the synthetic material on the blood pressure occurs promptly, hypertensive levels are not reached until after two to four weeks of constant therapy. It might be proper to point out here that treatment with the old adrenal cortex extract produced no marked changes in the blood pressure.

TABLE 2.—*Amount of Desoxycorticosterone Acetate Absorbed Daily from the Implanted Pellets as Determined by Removal of Pellets from Two to Six Months After Implantation*

Patient	Date of Implantation of Pellets	Weight of Pellets, Mg.	Date of Pellet Removal	Weight of Individual Pellets Removed, Mg.	Desoxycorticosterone Absorbed Daily, Mg.
1. D. G.	9/16/39	128	12/11/39	96.7	0.36
3. J. S.	7/27/39	126	9/25/39	110.9	0.28
				110.9	0.28
				114.9	0.20
				110.0	0.29
			1/24/40	68.1	0.32
				74.8	0.28
				78.6	0.27
				85.0	0.22

The effect of the synthetic drug on the pigmentation of Addison's disease is relatively slight and probably nonspecific in character. Following adequate treatment and after the general condition of the patient improved considerably there occurred some decrease in the intensity of the pigmentation. In no instance did the pigmentation entirely disappear. Whatever effect is exercised is probably the result of increased hydration of the patient.

The effect of the pellets is identical with that of the injection of the synthetic substance in oil. It must be

remembered, however, that when pellets are used the daily requirement of the desoxycorticosterone acetate is approximately from 60 to 75 per cent of that which is needed when the drug is given by injection. The pellets, then, have the advantage of being the more economical. However, after the pellets are implanted, control of the patient is difficult and the development of complications due to excessive medication requires surgical intervention to reduce the dosage. In deciding on the number of the pellets to be implanted in a patient with Addison's disease, the daily requirement must first be determined with intramuscular injections of the synthetic compound. Calculations are based on the fact that a pellet weighing from 100 to 150 mg. will liberate approximately 0.3 mg. of the drug daily (table 2). We feel that it is wiser to implant less than the required number of pellets and to supplement treatment with some additional salt by mouth (from 3 to 5 Gm.) daily. In this way the dangers of unfortunate complications are lessened. The dangers to be borne in mind in the use of this new drug are development of hypertension, edema and heart failure. The intelligent use of the synthetic compound requires careful clinical observation of the patient and adequate laboratory facilities for repeated blood electrolyte determinations. A word of caution must be said about indiscriminate use of this synthetic drug in various forms of asthenia. It is a powerful weapon, and until its pharmacologic actions are better understood its use should be restricted to patients with well defined Addison's disease.

SUMMARY

1. Five patients with Addison's disease were treated with intramuscular injections of desoxycorticosterone acetate in oil.

2. In four of these patients pellets of crystalline desoxycorticosterone acetate were subsequently implanted.

3. The disturbed blood electrolyte pattern is readily restored to normal with the aid of this new drug. It also exercises a marked salutary effect on the sense of well-being of the patients.

4. It produces marked increase in the blood pressure but exercises no effect on carbohydrate metabolism and on the pigmentation.

5. Pellets are more economical to use than are injections. They are, however, associated with greater danger of complications, since the control of the amount of the drug liberated is difficult and may require surgical intervention.

6. The dangers to be borne in mind with the use of the synthetic compound are development of hypertension, edema and heart failure.

7. Pellets weighing approximately 125 mg. liberate from 0.20 to 0.36 mg. of desoxycorticosterone acetate daily.

1155 Park Avenue.

Tuberculosis Death Rate.—In most parts of the world where statistics have been kept, the death rate from tuberculosis has been steadily declining for about one hundred years. About 1780 the estimated death rate from consumption in England was 650 per 100,000 living inhabitants. It is expected that the death rate in the United States will fall below 45 per 100,000 in 1940. According to Dublin, this will represent a decline of 37 per cent in the last ten years, and a decline of 61 per cent in the last twenty years. In forty years the death rate has dropped 76 per cent.—Webb, Gerald B.: Tuberculosis—Present and Future, *J. Lab. & Clin. Med.* **26**:287 (Nov.) 1940.

ROENTGENOLOGIC GROUP EXAMINATIONS FOR PULMONARY TUBERCULOSIS

IN NEGROES IN CHICAGO: PRELIMINARY REPORT

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Because of the high incidence of tuberculosis among persons who have been exposed to massive infection from others, x-ray examinations of such contacts have been a routine practice in the Chest Clinic of the University of Chicago since 1929. The convincing experience that early tuberculosis is most successfully found among those who, because of the absence of symptoms, are unsuspected led in 1932 to the initiation of a case finding program among students, faculty and hospital employees. The results were in keeping with those

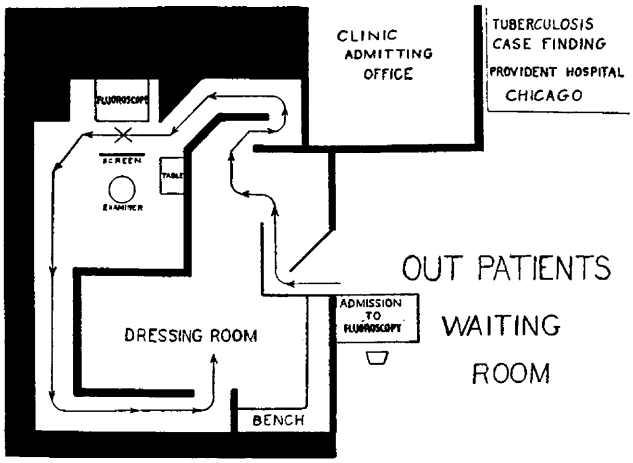

Fig. 1.—Arrows indicate route of patient through fluoroscopic plant.

reported from similar institutions and gratifying enough to continue the examinations as a university and hospital routine.

In 1934 the practice was extended to the expectant mothers seen in the clinic of the Chicago Lying-in Hospital because of the many unpleasant experiences with previously unrecognized tuberculosis among that group of patients and because they are an easily accessible group of healthy although physiologically strained persons. To date about 10,000 pregnant women have been examined. The published results from the first 4,000 indicated that slightly more clinically important tuberculosis is found by routine fluoroscopy of the chest than syphilis is by routine serologic tests.

SELECTION OF GROUP

Since the studies among the previously mentioned groups would not indicate the real proportions of the problem of unsuspected tuberculosis in the general population, it was desirable to gain access to still another

This work was financed by a grant from the Julius Rosenwald Fund.
From the Department of Medicine, University of Chicago, and the Provident Hospital.
Drs. R. W. Vines, J. L. Batty, H. H. McClanahan, and S. J. Gray of the Department of Medicine, University of Chicago, gave valuable assistance in the examinations.
Read before the Section on Preventive and Industrial Medicine and Public Health at the Ninety-First Annual Session of the American Medical Association, New York, June 12, 1940.