

## STREPTOMYCIN IN ACTIVE TUBERCULOSIS

QUESTION: What is the place of streptomycin in the treatment of the usual case of active pulmonary tuberculosis?

ANSWER: Streptomycin should be used in the early acute exudative types of pulmonary tuberculosis. The patient will be subjected to unnecessary risks and expense if streptomycin is given for the usual fibroulcerative case of pulmonary tuberculosis. At this time, streptomycin cannot be recommended for the treatment of (1) minimal pulmonary tuberculosis, (2) chronic fibroid or fibrocaceous pulmonary tuberculosis, (3) acute destructive and apparently terminal types of pulmonary tuberculosis or (4) chronic tuberculous empyema.

## TUBERCULOSIS SANATORIUMS

QUESTION (Dr. George J. Boines, Wilmington, Del.): Do you advise the use of streptomycin for general use in state tuberculosis sanatoriums?

ANSWER: It all depends on what you mean by "general use." I think that streptomycin should be available for selected cases in all tuberculosis sanatoriums.

## TUBERCULOUS SINUS

QUESTION (Dr. Victor Siegel, Red Banks, N. J.): Can streptomycin be used for tuberculous empyema sinus?

ANSWER: Many cases of tuberculous sinus are improved by streptomycin. How much good will result from the use of streptomycin in "tuberculous empyema sinus" will depend on the size and pathologic state of the empyema pocket and also on the state of the underlying pulmonary parenchymal disease.

## FAILURE OF STREPTOMYCIN IN EMPYEMA

QUESTION (Dr. Alexander Tish, Washington, D. C.): Why has streptomycin intrapleurally been of little or no value in tuberculous empyema and how can the failure be explained?

ANSWER: Streptomycin is of little or no value in tuberculous empyema because of the pathologic nature of this serious complication of pulmonary tuberculosis. It must be understood that streptomycin is helpful in early acute exudative pulmonary tuberculosis and has little or no effect on caseating lesions. It seems likely that in tuberculous empyema innumerable small as well as large caseating lesions are located in the pleura and in the underlying lung. Hinshaw thinks that the  $pH$  of the empyema fluids may interfere with the bacteriostatic action of the drug.

## HOW TO AVOID BAD EFFECTS OF STREPTOMYCIN

QUESTION (Dr. Sixto Y. Orosa, Bacolod, Philippines): Kindly suggest a plan for the administration of streptomycin for the treatment of pulmonary tuberculosis to avoid the bad effects on the patient.

ANSWER: In answering this question I should like it clearly understood that the suggested dose schedule has not been used long enough either to prove its efficacy or its harmlessness. I am convinced that daily doses of 2 Gm. for a period of one hundred and twenty days is too much. It seems possible already from animal experiment and clinical trials that a smaller daily dose in an intermittent schedule may be both effective and harmless. Suggested schedule of treatment: 1. Give 200 mg. of streptomycin intramuscularly every three hours; begin at 6 a. m., and give five doses in the twenty-four hours; not more than 1 Gm. daily. 2. Follow this schedule for two weeks; then stop for one week. Resume for two weeks, and stop for one week. 3. This schedule may be repeated for approximately one hundred and twenty days of actual administration of the drug. Time will tell whether this length of time and dose are optimal.

## TUBERCULOSIS OF THE SKIN

QUESTION (Dr. Michael Margolies, Coatesville, Pa.): Is streptomycin of value in treating tuberculosis of the skin?

ANSWER: Experience is lacking to give adequate answer to this question.

## "PROMIN" FOUND WANTING

QUESTION (Dr. S. A. Bolosky, Philadelphia): Has "promin" (sodium p,p-diaminodiphenylsulfone-N,N'-dixetrose sulfonate) by injection or "promizole" (4,2-diaminophenyl-5'-thiazolylysulfone) by mouth been given a long enough trial in pulmonary tuberculosis?

ANSWER: It is possible that combinations of streptomycin with another antibacterial agent such as "promin" or "promizole" may be more effective than the use of streptomycin or "promin" or "promizole" alone. A combination of streptomycin with some other bacterial agent may have the advantage of permitting the use of smaller and less toxic doses of streptomycin. Much work needs to be done on the synergistic action of antibacterial agents. "Promin" by injection and "promizole" by mouth have been weighed clinically and found wanting.

## WHAT'S NEW IN ENDOCRINOLOGY

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The object of this paper is to discuss the more important therapeutic advances that have occurred recently in the field of endocrinology. The most significant contributions have perhaps been those dealing with the use of antithyroid drugs and radioactive iodine in the treatment of toxic goiter and those dealing with the relation of androgens and estrogens to carcinoma of the prostate and breast respectively.

## THE PITUITARY

*Anterior Lobe.*—Our knowledge of pituitary function has increased still further. Interesting developments have been the isolation in Evans' laboratory in the University of California of an adrenocorticotrophic hormone and of a purified growth hormone. Preliminary reports on the effects of the adrenocorticotrophic hormone are contradictory. According to Thorn and others<sup>1</sup> it caused stimulation of all the known functions of the adrenal cortex in 2 patients with pronounced hypopituitarism. According to other observers<sup>2</sup> it does not affect the excretion of sodium and chloride. Further observations will be necessary to determine the precise status of this material. It is available at the present time for experimental use in only a few laboratories. Addison's disease is sometimes caused by atrophy of the adrenal cortex as a result of inadequate stimulation by the anterior lobe of the pituitary. On theoretical grounds it would be desirable to treat the disease in such instances with a suitable pituitary extract. No evidence is yet available as to whether prolonged administration of adrenocorticotrophic hormone results in the development of antibodies which inhibit its effect. Most pituitary extracts available in the past have not been suitable for routine clinical use because of the temporary nature of their action. Preparations of the thyrotrophic hormone will temporarily cause an

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1. Forsham, P. H.; Thorn, G. W.; Prunty, F. T. G., and Hills, A. G.: Clinical Studies with Pituitary Adrenocorticotropin, *J. Clin. Endocrinol.*, to be published.

2. Mason, H. L.; Power, M. H.; Rynearson, E. H.; Ciarraelli, L. C.; Li, Choh H., and Evans, H. M.: Results of Administration of Anterior Pituitary Adrenocorticotrophic Hormone to a Normal Human Subject, *J. Clin. Endocrinol.*, to be published.

increase in basal metabolism in many patients in whom there is any thyroid tissue capable of function. The metabolism always returns to its initial level or even a lower level with prolonged administration. The longest period of increase in basal metabolism which I have observed in man during the administration of thyrotropic hormone has been nine weeks.

Some of the newer preparations of pituitary gonadotropin in powder form have caused some stimulation of ovarian function. In a few women with secondary amenorrhea it has been possible to induce menstruation and in a few women with anovulatory menstrual cycles it has been possible to induce ovulation.

The new preparation of the growth hormone developed by Evans is of interest but so far has not been tried adequately in man. Preparations of the growth factor available up to the present have not proved very effective in clinical medicine. Engle and others<sup>3</sup> have observed temporary growth in a pituitary dwarf with a preparation of the growth factor.

The observations of Markee, Sawyer and Hollinshead<sup>4</sup> that the hypothalamus plays a major role in the release of luteinizing hormone from the anterior lobe of the hypophysis is of importance because of the influence that neurogenic factors appear to play in the control of endocrine function.

**Multiglandular Deficiencies Secondary to Hypopituitarism.**—In patients showing decided loss of pituitary function such as those with chromophobe adenoma of the pituitary and hypopituitary cachexia (Simmonds' disease) evidence has been obtained of the presence of hypothyroidism, hypofunction of the adrenal cortex and hypogonadism. Thus patients with chromophobe adenoma of the pituitary may show a very low level of basal metabolism, a low blood pressure, reduction in the concentration of sodium in the serum, increase in the secretion of sodium in the urine, reduction in the fasting blood sugar and various evidences of hypogonadism, including atrophy of the genitalia, amenorrhea and impotence. Patients with pronounced hypopituitarism sometimes show typical addisonian crises which have to be treated with the parenteral administration of large doses of adrenal cortex extract and the intravenous administration of sodium chloride and dextrose. They also suffer from attacks of hypoglycemia which are difficult to distinguish from addisonian crises. Patients with deficiency of the adrenal cortex secondary to hypopituitarism do not appear to become pigmented as frequently as patients with Addison's disease caused by destruction of the adrenal glands.

**Posterior Lobe.**—A few interesting reports have appeared on the posterior lobe of the pituitary, but no outstanding advances have been made. The most practical development has been further demonstration of the fact that diabetes insipidus may be controlled satisfactorily either by insufflation of posterior pituitary powder into the nasal cavities or by the intramuscular injection of "pitressin tannate in oil."

#### THE THYROID; TOXIC GOITER

Three important developments have occurred in the treatment of toxic goiter: (1) irradiation of the pituitary, (2) the use of antithyroid drugs and (3) the use of radioactive iodine.

**Irradiation of the Pituitary.**—A close relationship exists between the anterior lobe of the pituitary and the thyroid. The following effects of administration of the thyrotropic hormone have been observed in man: (1) increase in basal metabolism in all patients except those with complete myxedema; (2) production of thyrotoxicosis in patients with nontoxic goiter; (3) production of a syndrome resembling exophthalmic goiter in patients with a normal or slightly subnormal level of basal metabolism, and (4) increase in the severity of toxic goiter.

As has been pointed out, the increases in basal metabolism have always been temporary and have disappeared with continued administration over a period of eight to nine weeks. In a few patients with exophthalmic goiter, prolonged administration appears to have resulted in a cure. Following the initial increase, the basal metabolism has dropped to the normal level and remained there. Exophthalmos has not been reported in man as a result of the administration of the thyrotropic factor but it has been observed in various experimental animals. Hyperthyroidism secondary to hyperpituitarism has been noted in some patients with acromegaly, and hypothyroidism secondary to hypopituitarism has been noted in patients with chromophobe adenomas of the pituitary and in those with Simmonds' disease and anorexia nervosa.

The evidence available supports the hypothesis that the thyroid is only one link in the chain of events leading to the development of the symptom complex known as toxic goiter. Overstimulation by the pituitary appears to be an important factor. The cause of the stimulation of the pituitary has not been definitely determined but is probably related to some disturbance in the hypothalamus. Attempts to treat the disease by removing or destroying the thyroid probably do not attack the fundamental cause.

I have attempted to apply the knowledge of the pituitary-thyroid interrelations by irradiating the pituitary in a series of 43 patients with toxic goiter. A permanent remission was produced in about one third of them. These observations are of great importance from the standpoint of the mechanism which may be involved in the development of toxic goiter. However, it is not recommended that irradiation of the pituitary be used for the routine treatment of toxic goiter at the present time, chiefly because the percentage of cures is too low. Theoretically, this treatment might result in damage to other functions of the pituitary and to important structures in the base of the brain above the pituitary. Several years have now elapsed since these patients were treated and so far untoward early or late complications have not been observed.

**Antithyroid Drugs.**—Thyroidectomy, antithyroid drugs and radioactive iodine affect the thyroid directly and probably do not attack the underlying cause of the disease. In actual practice, control of the thyrotoxic phase of toxic goiter has proved to be a satisfactory form of treatment. The two antithyroid drugs most commonly used have been thiouracil and propylthiouracil. Propylthiouracil produces fewer toxic reactions than thiouracil but is not free from danger. These drugs have been used in two ways, namely, to treat the disease medically and to prepare patients for operation.

3. Engle, E. T., and others: Personal communication to the author.

4. Markee, J. E., Sawyer, C. H., and Hollinshead, W. H.: Activation of Anterior Hypophysis by Electric Stimulation in the Rabbit, *Endocrinology* 38:345-357 (June) 1946.

**Medical Management:** Sufficient time has not yet elapsed to determine the percentage of cures produced by thiouracil and propylthiouracil. The evidence available indicates that when the basal metabolism is maintained at the normal level with these drugs for periods of nine to twelve months, no recurrence of the disease is noted after omission of treatment in about 60 per cent of patients. The percentage of cures appears to be related to the length of time that the basal metabolism is maintained at the normal level before treatment is discontinued. The longer the drug is administered the higher the percentage of cures. Patients who are not cured by an initial course of treatment may show disappearance of the disease following a second or third course. Great caution must be used in concluding that toxic goiter has been cured by drug therapy because of the tendency of the disease to show spontaneous remissions and relapses and the observations of recurrence of the disease after many months of drug therapy. It will take several more years to determine the percentage of cures following adequate periods of administration. The development of these drugs represents an important advance in the treatment of toxic goiter, but they are not the final answer to the problem. In order for a drug to be satisfactory for medical management it must produce a cure in nearly all patients without producing toxic reactions. It is desirable to continue the observations already begun on the medical management of the disease in order to obtain more precise data on the percentage of cures. It is generally agreed that antithyroid drugs are valuable in the treatment of persistence and recurrence of toxic goiter following subtotal thyroidectomy and in the treatment of patients who present poor surgical risks; e. g., some older patients with cardiac decompensation.

**Surgical Management:** The introduction of anti-thyroid drugs, particularly propylthiouracil, represents an important advance in the preoperative preparation of patients with toxic goiter. With these drugs it is possible to eliminate the thyrotoxicosis completely in most instances, whereas iodine usually controls the disease only partially. Propylthiouracil is of the greatest value in the preoperative preparation of patients who have thyrotoxicosis in severe form, and these are the patients who have presented the most serious operative risks. With proper preparation, the mortality from thyroidectomy for toxic goiter has dropped almost to the vanishing point. Hospitalization of patients during the preoperative period is not necessary except in the presence of a crisis or some complication such as cardiac decompensation. Propylthiouracil is given until the basal metabolism drops to within normal limits. Iodine is then administered in addition to propylthiouracil for one week preceding operation in order to reduce hyperplasia and the danger of oozing of blood at the time of operation. Throughout the preoperative period the patient is given a diet high in calories. Operative procedures may be carried out a few days after admission to the hospital, thus greatly reducing the cost of hospitalization. Propylthiouracil may be discontinued at the time of operation but the administration of iodine is kept up until discharge from the hospital.

**Radioactive Iodine.**—The use of radioactive iodine represents an ingenious attack on the thyroid itself in patients with toxic goiter. Thyroxine contains 65 per

cent of iodine by weight. When small amounts of iodine are administered, the iodine is taken up almost entirely by the thyroid gland and, if radioactive, destroys many of the thyroid cells. An end result of such therapy is the development of areas of fibrosis in the thyroid gland. Myxedema may be caused by the administration of radioactive iodine to experimental animals. When given to patients with toxic goiter in proper amounts, it produces a cure in a large percentage of patients. As improvement sets in, the thyroid gland decreases in size. Patients receiving this form of treatment have not yet been followed long enough to determine the percentage of cures and the incidence of late complications, if any. No instance of carcinoma has been reported among patients followed up to the present time. In a few patients some temporary hoarseness has developed. Seidlin, Marinelli and Oshry<sup>5</sup> have recently reported striking improvement in a patient with hyperfunctioning metastases of adenocarcinoma of the thyroid. However, most carcinomatous cells do not produce much thyroxine and take up little radioactive iodine. This material is, therefore, not of much value in most patients with carcinoma of the thyroid.

**Malignant Exophthalmos.**—In most patients with exophthalmic goiter the prominence of the eyes becomes grossly less when the basal metabolism is reduced to the normal level. In a few instances the prominence of the eyes continues to increase in spite of adequate control of the thyrotoxicosis. Some observers are of the opinion that this phenomenon is more apt to occur if the basal metabolism is subnormal. The exophthalmos sometimes becomes so pronounced that it is impossible to protect the eyeball by closing the lids. Increase in the prominence of the eyes in spite of a normal or subnormal metabolism indicates that the cause of the disease is still active. Exophthalmos has been produced in experimental animals with thyrotropic factor from the pituitary. Dobyns<sup>6</sup> has recently described the organic changes in the orbit associated with the administration of thyrotropic factor to animals.

The treatment of malignant exophthalmos is unsatisfactory. Radical measures should be employed only when it is impossible to avoid complications with medical treatment, which includes the combined administration of iodine and desiccated thyroid and irradiation of the pituitary. Surgical relief of malignant exophthalmos involves removing part of the orbit, usually the roof and part of the lateral wall. Most surgeons are not enthusiastic about the results of surgical intervention.

#### THE PARATHYROIDS

Several interesting reports have appeared on the parathyroids but no really new developments have occurred. Parathyroid tetany is now a relatively infrequent complication of thyroidectomy and its treatment has been perfected. It has been clearly demonstrated that if this disorder is treated adequately as soon as it is recognized, it does not reduce life expectancy and complications such as bilateral cataracts do not develop. Small doses of dihydrotachysterol supplemented with

5. Seidlin, S. M.; Marinelli, L. D., and Oshry, E.: Radioactive Iodine Therapy: Effect on Functioning Metastases of Adenocarcinoma of the Thyroid, *J. A. M. A.* **132**:838-847 (Dec. 7) 1946.

6. Dobyns, B. M.: Studies on Exophthalmos Produced by Thyrotropic Hormone: Changes Induced in Various Tissues and Organs (Including Orbit) by Thyrotropic Hormone and Their Relationship to Exophthalmos, *Surg., Gynec. & Obst.* **82**:609-617 (May) 1946.



calcium salts by mouth provide the best form of treatment. Vitamin D in large doses is also effective in promoting absorption of calcium salts from the gastrointestinal tract and may be employed in the treatment of parathyroid tetany if dihydrotachysterol is not available.

#### THE ADRENALS

Some progress has been made in the development of new synthetic products which substitute for the adrenal cortex. The synthetic material desoxycorticosterone acetate affects sodium and potassium metabolism but not carbohydrate metabolism. In the form of pellets implanted subcutaneously it has proved to be a fairly satisfactory method of treatment. Not all patients tolerate the material well, and in them it is necessary to use adrenal cortex extract. Other products, such as 11-dehydrocorticosterone, are not available commercially but there is reason to believe that a synthetic product will soon be available that will affect sodium, potassium and carbohydrate metabolism. Sufficient data have now been collected to demonstrate that patients with Addison's disease may be kept alive for long periods of time. They do not have much reserve and are in great danger of having serious intercurrent infections at any time.

It has been my policy to rely on adequate substitution therapy with adrenal cortex extract or desoxycorticosterone acetate. Patients periodically have crises in spite of treatment that is adequate to maintain them under most circumstances. The reason for the failure is not clear. The maintenance requirement of patients varies greatly and their susceptibility to crises also shows great variation. When pellets of desoxycorticosterone were first used in treatment it was considered necessary to determine the maintenance requirement of patients by daily injections of this material. From the figure thus obtained for maintenance purposes, the known rate of absorption of this material from each pellet and the percentage of material supposed to be eliminated unused when it was given once a day by injection, it was possible to calculate roughly the number of pellets required for the initial implantation. It is now known that this procedure is impractical because pellets from different manufacturers vary in their rate of absorption. It is common practice at the present time to implant initially in the subcutaneous areolar spaces four pellets of 75 mg. each, or a total of 300 mg. If this amount is not adequate, additional pellets are implanted in increments of 150 mg. In most patients the initial implantation does not need to exceed 450 mg., but a few require as much as 600 mg. Before implanting pellets it is necessary to determine the response of patients to the daily parenteral administration of desoxycorticosterone acetate. A few patients do not tolerate this material well. Complications of its use are the development of hypertension, edema which may be generalized and the production of focal areas of necrosis in cardiac and skeletal muscle. These areas of necrosis in the heart muscle may so impair the circulation that death results.

Some progress has been made on the site of formation of the various principles of the adrenal cortex. Androgens are apparently produced in the reticular zone, while the cells of the outer layer appear to be devoted to the control of sodium and potassium metabolism. Numerous observations have appeared on the determination of 17-ketosteroids in the urine in health

and disease. In patients with Addison's disease the production of 17-ketosteroids is low because of destruction of the glands.

#### THE TESTES

*Hypofunction.*—Observations previously reported on the treatment of hypogonadism have been extended and confirmed. Chorionic gonadotropin has proved to be a satisfactory agent for stimulation therapy and testosterone propionate for substitution therapy. Chorionic gonadotropin will produce maximum stimulation of function only when the testes are capable of showing maximum response to stimulation. Persistence of hypopituitarism for a period of several years may result in irreparable damage to the testis so that it can no longer show a maximum response to stimulation. Under these circumstances, it is necessary to use testosterone propionate in order to produce the greatest possible change. One of the most important considerations in hypogonadism beginning early in life is the correct age for starting treatment. Treatment should be started at the age at which puberty normally sets in in order to insure maximum growth of the genitalia and prevent the skeletal abnormalities associated with hypogonadism. The male sex hormone will cause growth of the genitalia at any age in patients with a pronounced deficiency but the genital growth is not as great after as during the age of puberty. The uses and misuses of testosterone propionate have been discussed in a previous communication to this journal.<sup>7</sup> It is contraindicated in older men in whom the presence of carcinoma of the prostate is suspected.

*Sterility.*—A great deal of interest has developed on the subject of sterility. The male is sterile in infertile marriages in about 20 per cent of the patients. Stimulation of spermatogenesis in patients with secondary hypogonadism is not very satisfactory. In a few instances it is possible to cause some stimulation with some of the newer pituitary gonadotropins prepared in powder form. In determining the cause of sterility, it is advisable to investigate the male first, because it is comparatively easy to make a careful study of the production of spermatozoa.

#### THE OVARIES

*Menstruation.*—Knowledge of ovarian function has gradually increased. Rossman and Bartelmez<sup>8</sup> have recently reported that few women menstruate regularly at twenty-eight day intervals. Fluctuations of one to five days are to be expected, and the twenty-eight day period occurs only once in ten times. An unusually long or short cycle may occur at any time in any normal woman. Observations on the female macaque have indicated that preovulatory and postovulatory phases of the cycle vary independently of one another and that ovulation may occur at any time in either a long or a short cycle. Sevvitt<sup>9</sup> has also demonstrated that ovulation may occur at any time in the first half of the cycle, even during the latter part of menstruation. These observations clearly show that the calculation of the so-called safe period on the basis of the expected date of the next menstrual period is unreliable.

7. Thompson, W. O.: Uses and Abuses of the Male Sex Hormone, *J. A. M. A.* **132**:185-188 (Sept. 28) 1946.

8. Rossman, I., and Bartelmez, G. W.: Delayed Ovulation: Significant Factor in Variability of the Menstrual Cycle, *Am. J. Obst. & Gynec.* **52**:28-33 (July) 1946.

9. Sevvitt, S.: Early Ovulation, *Lancet* **2**:448-450 (Sept. 28) 1946.

There has been some development in pregnancy tests, although the Friedman modification of the Aschheim-Zondek procedure continues to be the most satisfactory method for routine clinical use.

An interesting observation has been the demonstration of changes in the early morning temperature during various phases of the menstrual period. In the premenstrual phase the temperature falls one or two days before the onset of menstruation. It falls further in the menstrual phase, sometimes to as low as 97 F., and then rises to between 98 and 99 F. In the follicular phase the temperature fluctuates between 98.4 and 99 F., and in the ovulatory phase it falls suddenly, usually about the fourteenth day before the onset of the next flow. It sometimes falls to as low a level as 97 F. and then rises suddenly. The luteal phase is characterized by a sustained elevation of temperature to 100 F. or more, which persists until one or two days before the next flow. There is a slight drop in temperature in the midluteal phase, corresponding to the estrogen peak. Determinations of temperature throughout the menstrual cycle have provided a simple method of determining the time of ovulation in many women.

*Abnormal Bleeding in the Treatment of the Menopause.*—Bleeding from the uterus may occur at any age following estrogenic therapy. This bleeding may sometimes be prolonged and excessive, particularly following large doses of estrogens, and may be particularly dangerous in women with fibroids. All women in whom estrogenic therapy is contemplated should have a careful gynecologic examination, and the presence of fibroids or carcinoma of the cervix or fundus are contraindications to its use. When estrogen-induced bleeding occurs it can usually be controlled with rest and ergonovine maleate but in occasional instances it may be necessary to perform a curettage to control it. In a few older women with fibroids the bleeding may be so prolonged and excessive that a hysterectomy is necessary.

In the treatment of the menopause an effort should be made to administer the minimum amount of estrogenic material that will control symptoms without inducing uterine bleeding. In actual practice it is not always easy to attain this ideal. Amounts of estrogen that are inadequate to control menopausal symptoms completely may induce uterine bleeding. If patients are carefully followed, those with fibroids and carcinoma of the cervix or fundus excluded, and the smallest dosage of estrogen administered that will control symptoms, treatment of the menopause is a safe and reliable procedure. Slight spotting which occurs periodically is not serious. Treatment should be discontinued until it disappears and then resumed. In most instances, when prolonged and excessive bleeding occurs with small doses of estrogenic material, it is best to discontinue treatment permanently.

*Hypogonadism Before the Menopause.*—Stimulation of the ovary with various gonadotropins is not very satisfactory. Chorionic gonadotropin is not nearly as effective in the female as in the male. Pituitary gonadotropin is sometimes effective in inducing menstruation in women with secondary amenorrhea and may cause ovulation in women with anovulatory cycles. In most instances substitution therapy with estrogenic material must be employed in the treatment of hypogonadism in

the female. There is some difference of opinion concerning the most effective estrogen. For most purposes, estradiol in some suitable combination such as the benzoate or the dipropionate appears to be the most satisfactory product, but there are many estrogenic preparations on the market which produce excellent results. In the female, as in the male, the optimum time for the treatment of hypogonadism is the age of normal puberty. It is only by starting treatment at this age that maximum genital growth can be induced and skeletal disproportions prevented. The difficulty is that the diagnosis of hypogonadism early in puberty is much more difficult in the female than in the male because the development of the ovary cannot be determined as readily as the development of the testis. When hypogonadism is the result of a primary defect of the ovary, it is permanent and treatment is necessary during a large portion of the patient's life. The ideal form of treatment is the cyclic administration of estradiol and progesterone in a manner that simulates their normal production, so that periodic uterine bleeding is induced.

#### HORMONE ASSAYS

The time has arrived when the practice of endocrinology cannot be carried out adequately without proper laboratory facilities. For purposes of correct diagnosis and checks on therapy, it is necessary to have available facilities for determining the production of various hormones and the estimation of the concentration of various other substances in the blood and urine. The determination of the basal metabolism is also an essential of any adequate endocrine laboratory. It is important to be able to determine the production of follicle-stimulating hormone, androgens, estrogens, adrenal cortical steroids, etc. Facilities for determining the presence or absence of pregnancy (chorionic gonadotropin) are indispensable. It is essential to be able to make simple chemical tests—for example, determinations of sugar, sodium, potassium, calcium, phosphorus, phosphatase, total protein, albumin, globulin, nonprotein nitrogen, uric acid, creatine and creatinine—in blood and urine. Roentgen examination of the skeleton is essential in determining the effect of glandular abnormalities on growth. Gynecologic examination, endometrial biopsies and examination of the vaginal smear may furnish important information.

#### RELATION OF HORMONES TO CARCINOMA

*Carcinoma of the Prostate.*—A few years ago Huggins<sup>10</sup> reported that orchiectomy sometimes produced striking improvement in patients with carcinoma of the prostate. Metastases in bone sometimes disappeared after this procedure, on the basis of roentgen examination. Huggins originally reported the results of orchiectomy in 20 patients with advanced carcinoma of the prostate. All had demonstrable metastases or local infiltration beyond the prostatic capsule. In 2 patients there was no obvious improvement from the operation. In the remainder clinical improvement was obtained for varying periods postoperatively. Eleven patients died during the first two years after orchiectomy and 4 others died within thirty-six to sixty-three months. Two deaths were the result of intercurrent infection. The median survival time for the 15 fatal

10. Huggins, C.: Prostatic Cancer Treated by Orchiectomy: Five Year Results, J. A. M. A. 131:576-581 (June 15) 1946.

cases was sixteen months, with improvement during eleven months of this period. Five patients survived more than five years after orchiectomy. Of these, 4 showed no signs of disease and 1, although apparently well, had a tumor mass in the region of the seminal vesicles. It would be premature to suggest that actual cure of the disease has been achieved in any case. Huggins and Scott<sup>11</sup> have recently reported the effects of bilateral adrenalectomy in 4 men with rapidly growing metastatic carcinoma of the prostate after orchiectomy had failed to arrest the malignant growth. Two men survived only thirty-six and fifty-four hours after complete adrenalectomy. The third patient lived eleven days and the fourth patient one hundred and sixteen days. Adrenalectomy did not appear to prolong life in these patients. The urinary 17-ketosteroids fell to a level of less than 2 mg. per day. This observation furnishes the first direct proof that the chief sources of urinary 17-ketosteroids are actually the gonads and the adrenals. The advance of the malignant process in a man with low androgenic activity suggests a factor apart from the stimulating effect of testicular and adrenal androgens. To this factor Huggins has given the name "androgen independence." Huggins has expressed the opinion that androgen may be necessary for the development of carcinoma of the prostate but that once the process is set in motion it may continue without androgenic stimulation.

Reports are appearing from various clinics on the effect of surgical castration and functional castration with estrogens in patients with carcinoma of the prostate. All observers are agreed that striking initial improvement is produced in most of the patients and most observers feel that life is prolonged. Many patients have died of carcinoma of the prostate after initial improvement. Sufficient time has not yet elapsed to determine whether castration ever produces a permanent cure. It is Huggins' opinion that bilateral orchiectomy is a more effective procedure than the administration of diethylstilbestrol.

*Carcinoma of the Breast.*—For years it has been known that occasionally in women with carcinoma of the breast removal of both ovaries produces some improvement. Adair and others<sup>12</sup> have recently reported that functional castration of women by the use of testosterone propionate in oil often produces striking clinical improvement. This improvement may consist in a decided reduction in the size of the local lesion in the breast, a decrease in the size of the metastases in the neighboring structures and an improvement in the metastatic lesion in bone.

The results are by no means as striking as those of castration in carcinoma of the prostate. It is the impression of some workers in this field that testosterone propionate is primarily of value when bony metastases are present. For reasons which are not clear at the present time, after the age of the menopause estrogens are said to produce some improvement in soft tissue metastases, whereas before the menopause they are supposed to aggravate the condition. As time has gone on, most patients have died of carcinoma of the breast. Results, while interesting, are not nearly as conclusive as those in carcinoma of the prostate.

Carcinoma of the breast may be produced by administration of estrogen in certain mice, but, up to the present time, there is no evidence that the administration of estrogenic material causes carcinoma of the breast in women. Many women have been frightened through articles appearing in the lay press implying that use of estrogenic material in the treatment of the menopause is harmful and likely to produce carcinoma of the breast. It is significant that among the large numbers of women receiving estrogens for treatment of the menopause, carcinoma of the breast is rarely noted. The danger of development of cancer of the breast can therefore scarcely be used as an argument against the treatment of the menopause with estrogen.

#### THE PANCREAS

No important development has recently taken place in knowledge of the internal secretion of the pancreas. The use of various insulins has been perfected and gradually more is being learned about islet cell tumors of the pancreas which produce hypoglycemia.

One interesting observation has been that by Dixon and others<sup>13</sup> at the Mayo Clinic and by Ricketts, Brunschwig and Knowlton<sup>14</sup> at the University of Chicago on the effect of total pancreatectomy in a patient with diabetes mellitus. They noted that the total insulin requirement was unaffected by this operation.

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#### ABSTRACT OF DISCUSSION

##### TREATMENT OF THE MENOPAUSE

QUESTION: What is the most satisfactory endocrinologic treatment of the menopause?

ANSWER: About 40 per cent of women have no untoward symptoms following cessation of menstruation. These women require no treatment. The remaining 60 per cent have symptoms which vary in intensity from patient to patient. In some women the symptoms are severe and include frequent hot flushes, palpitation, nervousness and various psychic disturbances such as persistent depression and paranoia. The duration of the symptoms varies from a few months to many years and the duration of treatment varies accordingly. The best method of treatment is to give the minimum amount of estrogenic material that will control symptoms. There are a variety of synthetic and natural estrogens available for this purpose. Of the synthetic estrogens, diethylstilbestrol has been used most widely. The minimum dose that will control symptoms completely varies from 0.25 mg. to 1.5 mg. daily. Most women do not require more than 0.5 mg. daily. In these doses diethylstilbestrol rarely produces toxic effects, although various claims of superiority have been put forth for other estrogens, such as dienestrol. The synthetic estrogens possess the advantage of being very effective by mouth. Of the natural estrogens the most effective probably is estradiol. It is usually given in the form of the benzoate or the dipropionate and is more effective when administered intramuscularly than when given by mouth. The minimum dose required to control symptoms varies from 1.67 mg. every two weeks to 5 mg. twice a week. It is important to carry out a careful pelvic examination before instituting estrogenic therapy for the menopause. This form of treatment is contraindicated in women with carcinoma of the cervix and in most patients with uterine fibroids. In women with fibroids excessive bleeding may start, either during estrogenic therapy or after its withdrawal. Even in women whose uterus appears to be normal prolonged and excessive

11. Huggins, C., and Scott, W. W.: Bilateral Adrenalectomy in Prostatic cancer: Clinical Features and Urinary Excretion of 17-Ketosteroids and Estrogen, *Ann. Surg.* **122**:1031-1041 (Dec.) 1945.

12. Adair, F. E., and Hermann, J. B.: Use of Testosterone Propionate in Treatment of Advanced Carcinoma of the Breast, *Ann. Surg.* **123**: 1023-1035 (June) 1946.

13. Dixon, C. F.; Comfort, M. W.; Lichtman, A. L., and Benson, R. E.: Total Pancreatectomy for Carcinoma of the Pancreas in a Diabetic Person, *Arch. Surg.* **52**:619-639 (June) 1946.

14. Ricketts, H. T.; Brunschwig, A., and Knowlton, K.: Effects of Total Pancreatectomy in Patient with Diabetes, *Am. J. Med.* **1**: 229-245 (Sept.) 1946.



bleeding may follow the prolonged administration of estrogen in large doses. Treatment should be interrupted every three or four months to determine whether it is still necessary and the patient should be followed carefully during treatment. It is probably best not to administer estrogen to any woman in whom the presence of carcinoma of the breast is suspected although it has been claimed that in women after the age of the menopause estrogenic therapy may be of some value in reducing the size of soft tissue metastases.

#### TREATMENT OF OBESITY

QUESTION: Are endocrine products useful in the treatment of obesity?

ANSWER: Obesity may or may not be associated with endocrine deficiencies although the presence of hypogonadism in patients with obesity is common. Desiccated thyroid may be employed in moderate doses (2 to 4 grains [0.12 to 0.25 Gm.] daily) under careful supervision to supplement a weight-reducing diet. Patients must be followed carefully during the administration of this material because in some instances symptoms of intoxication develop with small doses. Great care must be taken to avoid self medication with thyroid products. In adolescent boys suffering from the Fröhlich syndrome the administration of chorionic gonadotropin may produce a complete transformation without a weight-reducing diet. As a result of the stimulation of the production of the male sex hormone the muscles develop, shoulders become broader, hips narrower, and breasts and abdomen smaller. If the obesity associated with this condition is severe, it is necessary to supplement the administration of chorionic gonadotropin with the administration of a weight-reducing diet.

#### EXTRACTS OF ADRENAL CORTEX

QUESTION: For what conditions are extracts of adrenal cortical substances effective?

ANSWER: The most important indication for the use of adrenal cortex extract is the presence of Addison's disease. It is the only material that is effective in the treatment of a crisis of this disorder, whereas for maintenance therapy the synthetic material desoxycorticosterone acetate is preferred because of its low cost and the fact that it may be implanted subcutaneously in the form of pellets, thereby eliminating the necessity of daily injections. There are many reasons for believing that the cortex of the adrenal gland produces a material which plays an important role in the resistance of the body to trauma and infection. Administration of adrenal cortex extract has accordingly been tried in the treatment of shock, in the treatment of severe infections to supplement specific substances and in the treatment of patients who have severe reactions following surgical procedures. There are data which suggest that adrenal cortex extract is of some value in the treatment of these conditions. The cost of the material and its rather limited supply have prevented its adequate trial in conditions which have just been mentioned. In some instances the doses used have been too small to produce much improvement. In the presence of shock and overwhelming infection it is probably necessary to give the material in doses of not less than 10 cc. per hour.

#### RADIOACTIVE IODINE

QUESTION (Dr. Fred Kauffmann, Canton, Ohio): In what way can radioactive iodine be handled for practical purposes?

ANSWER: Radioactive iodine is not yet ready for routine clinical use. To treat patients with toxic goiter satisfactorily with this material there must be an adequate setup for measuring the dose administered and the amount of material taken up by the thyroid gland and the rate at which it disappears. The equipment necessary for this purpose is relatively expensive and its application requires specially trained personnel. Radioactive iodine has therefore been used in only a few clinics up to the present time. All radioactive material has to be handled with the greatest care because of serious consequences which may follow overexposure to the powerful rays emitted.

#### ABSTRACT OF DISCUSSION

*The answers to the following questions were by Dr. Chester S. Keefer, Boston, whose original presentation comprised a lantern demonstration and was therefore not suitable for publication.*

##### PENICILLIN BLOOD LEVELS

QUESTION (Dr. L. H. Hirsh, Milwaukee): What is the relation of blood levels to tissue levels in use of penicillin?

ANSWER: Penicillin diffuses into red blood cells in about 10 per cent of the concentration of that in the plasma. Very small amounts diffuse into the cerebrospinal fluid, even after large intramuscular or intravenous injections of penicillin. Penicillin can be found in pericardial, peritoneal, pleural, joint and edema fluid. The concentration in general is lower than that found in the blood at the same time. Little, if any, diffuses into the tears or saliva, or the pancreatic juice or the milk. It passes through the placenta from mother to infant. The amount present in placental cord blood is approximately 40 per cent of that found in maternal serum. It has also been ascertained that penicillin diffuses into the kidney, small intestine, lung, buccal mucosa, bile, skin, liver, adrenal glands, pancreas, heart, voluntary muscle and spleen. Practically none is found in the brain and bone marrow, even one hour after intravenous injection of fairly large doses. The dura mater, cornea, lens and vitreous humor contain no penicillin, and nerve tissue only traces. In brief, penicillin diffuses into various organs of the body in much lower concentration than that found in the plasma.

##### PENICILLINASE

QUESTION (Dr. A. C. Worley, Fort Wayne, Ind.): Do body cells develop penicillinase? If so, how long does resistance last?

ANSWER: There is no evidence that the body cells develop penicillinase. Penicillin is not inactivated by any of the body fluids, pus or necrotic tissue. Some bacteria, notably the Staphylococcus and the gram-negative bacilli, may produce penicillinase.

##### MIXTURES OF ANTIBIOTICS

QUESTION: Can streptomycin and penicillin be mixed in the same syringe?

ANSWER: Yes, there is no contraindication to mixing the two together for simultaneous injection.

##### BACITRACIN

QUESTION: Are there any new effective antibiotics?

ANSWER: The only new antibiotic that has been investigated on a limited scale is bacitracin. Dr. Meleney and his associates have used bacitracin locally for the treatment of infected wounds. It has the same general scope, as far as bacteria are concerned, as penicillin.

##### TREATMENT OF ORDINARY SORE THROAT

QUESTION: Do you think it advisable to treat ordinary sore throat with penicillin and/or sulfonamide drugs?

ANSWER: Yes. Most instances of sore throat are due to hemolytic streptococcus infection. Penicillin and/or the sulfonamide drugs can prevent suppurative complications and reduce the total number of days of illness.

##### STREPTOMYCIN NOT INFECTIOUS

QUESTION (Dr. Erling S. Wedding, Brooklyn): Have any strains of streptomycin ever been demonstrated to be pathogenic to man or experimental animals?

ANSWER: I do not know of any cases in which Streptomyces griseus has been responsible for infection in man.

##### ABSCESS OF THE LUNG

QUESTION (Dr. William Klein, New Brunswick, N. J.): Have you found a greater incidence of pulmonary abscesses following the use of penicillin in pneumonias?

ANSWER: From a study of the large number of cases reported to the Committee on Chemotherapeutic and Other

Agents of the National Research Council, there is no evidence that the use of penicillin in the treatment of pneumonias is followed by a larger number of pulmonary abscesses.

#### ORAL PENICILLIN

QUESTION (Dr. Charles P. Ryland, Washington, D. C.): Please discuss the efficacy of penicillin orally.

ANSWER: At least three to five times as much penicillin should be given by mouth as is given parenterally. It has been found to be extremely effective in the treatment of pneumococcus pneumonia, gonococcal urethritis, hemolytic Streptococcus infections of the throat and pharynx, and other mild or moderately severe infections that respond to penicillin.

#### STREPTOMYCIN TIME-DOSE RELATIONSHIP

QUESTION (Dr. Belle Jacobson, New Rochelle, N. Y.): Is it necessary to give streptomycin every three hours in the treatment of tuberculous meningitis?

ANSWER: There is not enough information available concerning time-dose relationships to make any precise statement concerning the time interval between the injections of streptomycin in the treatment of tuberculous meningitis. It is not unlikely that injections every six hours throughout the day will be adequate, for the reason that streptomycin is excreted by the kidney much more slowly than is penicillin.

#### UNDULANT FEVER

QUESTION (Dr. P. Blair Ellsworth, Idaho Falls, Idaho): What is the latest treatment for undulant fever?

ANSWER: The best results that have been reported in the treatment of undulant fever, particularly the early cases—that is to say, patients who have been ill for less than two weeks—have been from the combination of sulfadiazine and streptomycin. Streptomycin should be continued for at least four weeks in amounts of at least 2 Gm. a day; sulfadiazine should be continued for a similar period of time, depending on the reaction of the patient. In the chronic cases of undulant fever, the evidence is far from convincing that any of the chemotherapeutic agents are responsible in shortening the course of the disease.

#### INTRASPINAL INJECTIONS

QUESTION (Dr. George Vryonis, Alexandria, La.): What dilutions of penicillin and streptomycin should be used in intraspinal injections? What undesirable results may follow?

ANSWER: Penicillin should be diluted so that not more than 1,000 to 2,000 units per cubic centimeter of isotonic solution of sodium chloride are used. The maximum dose should be not more than 25,000 to 50,000 units in a twenty-four hour period. For streptomycin, the maximum dose in a twenty-four hour period should be 50 to 100 mg., diluted in 10 to 20 cc. of isotonic solution of sodium chloride. With low dilutions and a volume of solution that is equal to that which has been withdrawn after lumbar puncture, there are usually no undesirable effects. If on the other hand, one uses high concentrations and small amounts, headaches, meningismus and, rarely, convulsions may follow.

#### PERTUSSIS

QUESTION (Dr. Benjamin Feldstein, New York): Is streptomycin of value in the treatment of pertussis?

ANSWER: So few patients with pertussis have been treated with streptomycin that it is impossible to answer this question with certainty. A few patients with pertussis associated with pneumonia and fever have been treated with streptomycin with striking results. There are several studies under way at present, so that more information concerning the value of streptomycin in pertussis will be forthcoming.

#### COMBINED INJECTIONS

QUESTION (Dr. H. H. Schuman, Springfield, Mass.): Is there any contraindication to using both penicillin and streptomycin in a single combined injection?

ANSWER: There is no contraindication to using both substances in a single combined injection. They should both be made up freshly before injection.

#### TOLERANCE TO PENICILLIN

QUESTION (Dr. A. I. Rosenblum, Chicago): What is the present status regarding the development of tolerance to penicillin following repeated uses for different diseases?

ANSWER: There is no evidence that the use of penicillin repeatedly builds up a tolerance on the part of the patient to its effective use when infections occur.

#### DISTILLED WATER OR SALINE SOLUTION

QUESTION (Dr. L. C. Moeris, Chicago): Is it desirable to administer streptomycin in distilled water rather than in saline solution?

ANSWER: Streptomycin may be administered either in distilled water or in saline solution. There is some evidence that mixing streptomycin with isotonic solution of sodium chloride decreases its activity. This has been demonstrated in vitro, but so far there is no evidence that using streptomycin in saline solution for the treatment of infections in man has decreased its potency.

#### PROPHYLAXIS OF RHEUMATIC FEVER

QUESTION (Dr. J. L. Hrdina, Cicero, Ill.): Do you recommend the daily oral use of penicillin in the prophylaxis of rheumatic fever for long periods, say two to four years' continuous use?

ANSWER: No one has had any experience with the daily oral use of penicillin for two to four years continuously. There is some evidence, based on experience over the last two years, that penicillin given in amounts of 50,000 units twice daily will prevent Streptococcus sore throat when patients are under carefully controlled conditions. In this way the incidence of the recurrence of rheumatic fever may be reduced.

#### LEGAL LIABILITY

QUESTION: What legal liability can a physician incur at this time, knowing the possible permanent disabilities the patient will incur with the use of streptomycin?

ANSWER: I do not know. This is a matter that should be taken up with legal counsel in order to get a specific opinion.

#### ALLERGIC REACTIONS

QUESTION: I suggest a plea for more accurate reports on the allergic reactions following the injection of penicillin in wax and peanut oil. The incidence seems higher than 5 per cent and the distress to patient and physician much higher than 50 per cent. Can a different menstruum be made?

ANSWER: No menstruum has been developed other than peanut oil and white wax for adequately delaying the absorption of penicillin from local deposits. In a controlled series of cases studied by Dr. Harry Dowling in Washington, D. C., the incidence of allergic reactions following the injection of penicillin in oil and wax was 5 per cent. This is a personal communication from the investigator.

#### ANTIBIOTICS AND THE COMMON COLD

QUESTION: Is it worth while to give antibiotics in the treatment of the common cold or influenza?

ANSWER: There is no evidence that any of the antibiotics influence the course of influenza or the common cold.

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**A Vaccination Record.**—In less than a month more than 6,300,000 people were vaccinated in New York City, over 5,000,000 of them within the two week period following the appeal for universal vaccination made by the Mayor. Never before had so many people in one city been vaccinated in such a short time and on such short notice. Thanks are due to the press and radio for giving so generously of their space and time to bring necessary information to the public. Had it not been for them and for the intelligent cooperation of the public and the generosity of private physicians and volunteer workers, notably from the American Red Cross and the American Women's Voluntary Services and former Air Raid Warden groups, it would have been impossible to have achieved this remarkable record.—Weinstein, Israel, M.D., An Outbreak of Smallpox in New York City, *American Journal of Public Health*, November, 1947.