investigations. Gordon discovered that when extracts made from glands taken from cases of Hodgkin's disease are injected intracerebrally into rabbits, symptoms of encephalitis are regularly produced. Although Gordon failed to transmit the disease from rabbit to rabbit he believes that his experiments demonstrate the virus nature of Hodgkin's disease. In our rabbits the symptoms have closely resembled those observed by Gordon, but there are differences of a quantitative kind, and there are differences in the incubation period and clinical picture. Whether these differences are due simply to differences in material or in technique can be determined only by further inquiries. We refrain from theoretical discussion until it is settled whether or not encephalitis produced by lymph glands from cases of Hodgkin's disease is identical with that produced by normal human bone marrow.

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A CASE OF ADDISON'S DISEASE

BY

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The advent of suprarenal cortical extracts into the realm of practical therapeutics has aroused new interest in Addison's disease. It is unnecessary here to recapitulate the history of the introduction of this form of substitution therapy or to deal in detail with the results obtained by American observers and by others in this country and on the Continent. References to most of the published work are given by Levy Simpson¹ and G. A. K. von dem Borne.²

EFFECT OF CORTICAL EXTRACT ON SYMPTOMS

While all are agreed upon the dramatic results which follow the administration of cortical extracts in the crises of Addison's disease, there is a considerable difference of opinion among many writers as to the more remote results which can be obtained. It has been held that the administration of cortical extracts is followed by the amelioration of all the several groups of symptoms—muscular, cardiovascular, gastro-intestinal, psychological, and pigmentary. The asthenia, wasting, sense of fatigue, dysphonia (Segre), poor heart action, subnormal temperature, hypersensitivity to cold, lowered metabolic rate, anorexia, nausea, retching, vomiting, hiccup, yawning, lethargy, insomnia, photophobia, irritability, negativism, pessimism, involuntary crying and grimacing, abdominal and loin pain, and lowered resistance to infection—all tend to disappear. Pigmentation is said by many but not all observers to follow suit, and the same in regard to the lowered blood pressure and hypoglycaemia.

It seems certain that the blood pressure is raised by the giving of cortical extracts during the acute crises of the disease, when very low readings may be found; but it is by no means clear whether this is a direct or an indirect effect. During stationary phases little effect, if any, may be seen. The symptoms resembling those of hypoglycaemia, associated with a drop in the blood sugar, which occur just before and during a crisis, are relieved by cortical extracts, and normal blood sugar readings are restored. Pigmentation is said to be little or in no way altered by treatment in many cases. Britton, Harrop,

and Weinstein³ held that these three symptoms are quite uninfluenced by the administration of cortex, and it is of interest to recall the fact that these three phenomena were considered to form no part of the symptom-complex determined by adrenalectomy in dogs—a fact perhaps indicating the caution necessary in interpreting the symptoms in Addison's disease in man in terms of the results of animal experiment. On the other hand, later work suggests that the syndrome in animals may be more analogous to that in man than was at first supposed. The signs of impaired renal function, as evidenced by albuminuria and high blood urea, clear up under treatment with cortical extracts; the lowered creatinine excretion and rise in urinary creatine may also be corrected, but no diminution of the raised blood cholesterol is effected.

Despite the initial improvement which has taken place in practically all cases treated with cortical extracts—and cortical extracts are a life-saving remedy in the acute crises of the disease—complete restoration to the normal has never, according to von dem Borne, been attained. Experience at the Mayo Clinic showed that, even though very considerable improvement was temporarily established and life prolonged, death inevitably followed. Other cases, it is true, have been reported in which health has been restored and maintained for many months, even after cessation of treatment, but the ultimate results have not been made known and the underlying pathological condition has remained unrevealed. Apart from the evidence sometimes afforded by radiography (calcification in some tuberculous cases) there is no certain method of discriminating, during life, between those cases (70 to 90 per cent.) in which the lesion is tuberculous and those in which there is said to be a simple atrophy. Levy Simpson, however, holds that all the symptoms of Addison's disease tend to clear up under treatment with cortical extracts given in sufficiently large doses, and that health can be restored and maintained.

PREPARATION OF CORTICAL HORMONE

Failure to obtain better results in man in the past have been due in part to the difficulty in assessing correct dosage. Suprarenal extracts have certainly differed widely in their hormonal content, and it seems doubtful if any very satisfactory means of standardization has yet been devised. W. W. Swingle and J. J. Pfiffner⁴ have defined a dog unit (D.U.), using as criteria "the maintenance of body weight and blood level of non-protein nitrogen (or urea)," and in the experimental animal obtained complete control after adrenalectomy by giving cortical extracts which possessed an adrenalin content of only 1 part in 1,250,000 to 2,500,000; but whether such a method of standardization is applicable for man remains uncertain. The same is probably true of the method of biological assay in rats adopted by N. V. Organon, for the preparation "cortin" (J. W. R. Everse and P. de Fremery; A. A. Adler, J. W. R. Everse, P. de Fremery, and A. Luchs; and M. Tank and A. W. M. Pompen).

The mechanism whereby the internal secretion of the adrenal cortex exerts its normal functions on the body is unknown. It has been suggested that this gap in our knowledge will be filled when it is possible to prepare the cortical hormone in a pure state. It is by no means certain that there may not be more than one cortical hormone. The problem, indeed, may be a more complicated one than would appear at first sight. In man none of the biochemical tests which may be carried out would appear to have proved very satisfactory as a means of evaluating the results of cortical extract therapy. Such tests are useful, though possibly not more useful than a study of the patient's reactions to treatment

may prove, even though, according to Levy Simpson, they "constitute crude indications" only.

It has been suggested that some of the symptoms of Addison's disease are not directly due to cortical insufficiency, but rather to an intoxication of an unknown nature produced secondarily; but there is no evidence of value upon this point. In view of the breast changes which occurred in the case described below the possible connexion between the suprarenal gland and sex characteristics may just be mentioned. The syndrome associated with hypernephromata is well known. H. L. Cecil³ has described the cases of two males, aged 26 and 27 years, who showed pronounced changes in the direction of femininity in the presence of hypernephroma. The results of animal experiment have yielded little of value. Corey and Britton found that intraperitoneal injection of cortical extracts in male and female rats led to premature maturation of the sex glands, uterine hypertrophy, and enlargement of the pituitary in the latter, and but slight changes in the testes of the former. Kaplan's results were variable, and no conclusions could be drawn from them.

DOSAGE OF EXTRACTS

In regard to the dosage of cortical extracts, Hartman in America advised 10 c.cm. intravenously during a crisis, followed by 5 c.cm. intramuscularly, of a preparation called "cortin" (1 c.cm. = 40 grams of cortex). Rowntree, Greene, Ball, and Swingle⁴ found daily doses of 60 c.cm. intravenously to be necessary during the initial treatment of the crisis. Levy Simpson, using eucortone (Allen and Hanburys: 1 c.cm. = 30 grams of cortex), considered that large doses were necessary throughout the twenty-four hours for the first few days, then 20 c.cm. until stabilization had been effected, followed later by 10 c.cm. a day intramuscularly and a maintenance dose of half that amount. These maximum doses would appear to fall short of what would be comparable to the dose for an animal: judging by animals the daily dose for man should be 90 c.cm. The above-mentioned doses appear to have been most generally employed, but owing to the considerable cost there is perhaps always a tendency to use too small an amount. Failure to increase in weight or any tendency for symptoms to reappear is a sign of inadequate treatment.

The difficulties entailed by a form of treatment necessitating one or more intravenous injections are sufficiently obvious. Intramuscular injections may be substituted, but are certainly not so safe in a crisis, and a larger dose is necessary. The same is true in greater degree with administration by the mouth. Britton, Flippin, and Silvette have shown that giving cortical extract in this way will prolong indefinitely the life of adrenalectomized cats. Animals showing complete refusal of food begin to feed an hour after taking the extract, followed by complete recovery from the symptoms and of the high blood non-protein nitrogen and the low blood sugar induced by the operation. Eucortone is effective when given by mouth in doses three to five times as great as those given intravenously, but when it is remembered that eucortone costs 90s. for 50 c.cm., such a method of administration is ruled out. The same is true of eschatin (Parke, Davis and Co.: 1 c.cm. = 30 grams of fresh cortex). A trial preparation made by Allen and Hanburys for oral administration in doses of 15 c.cm. (= 5 grams of cortex) was found to have little value.

While in practice, therefore, cortical extracts have a place in the treatment of Addison's disease in which the results are specific and dramatic, further research, it is hoped, will lead to the discovery of a less costly preparation which will be more efficacious during the prolonged stages of the disease. It has been thought possible that cortical extracts as at present prepared do not contain

some essential derivative of the adrenal gland. Harrop and Weinstein⁵ are among the few who prefer to use whole-gland extracts. In the case reported below dried whole-gland suprarenal (Armour), in doses of 90 to 120 grains (= 6 to 8 grams) fresh gland a day at a cost of 1s. to 1s. 6d. containing 0.4 to 0.6 per cent. adrenaline, appeared to possess advantages worthy of further trial. The following case, unfortunately incomplete, illustrates some of the points discussed above.

HISTORY OF CASE

The patient was a Frenchman aged 21. There was nothing worthy of note in the family or in the past history of the man; no history of tuberculosis. The earliest symptom of the present illness was pigmentation of the skin. In youth, though the patient was a black-haired, brown-eyed type, the skin is said to have been fair. Some five to six years ago pigmentation was first noticed, since when it has been progressive until the present time, though it is thought that variations in the depth of the colour have occurred from time to time.

In September, 1931, he commenced his military service in the French Army (Strasbourg), and was at that time well and strong and able to carry out his duties. About a year later, August, 1932, he began to feel weak; he was easily tired, and there was loss of appetite and weight. On September 4th, 1932, he was admitted to a military hospital. His symptoms included muscular weakness, giddiness, somnolence, abdominal pain, and attacks of vomiting. He had lost 2 stone in weight, and the blood pressure was said to be so low that readings could not be taken. He was treated, with some improvement, by the administration of adrenaline by mouth, 40 drops in water being taken in divided doses throughout the twenty-four hours. At the end of November, 1932, he was discharged "unfit" from the French Army and came over to England to join his brother. He remained in much the same condition, but on January 20th, 1933, had an attack of syncope, for which he was admitted to the Mile End Hospital. The immediate treatment consisted in the administration of 10 per cent. glucose solution intravenously. The blood pressure was then found to be 75/42, and the blood sugar 88.9 mg. per cent. Twelve days after admission, February 1st, injections of eucortone, 15 c.cm. intravenously, were begun, with immediate improvement—the appetite returned, nausea disappeared, he felt brighter, and the blood pressure was read at 85/50.

Clinical and Laboratory Findings

On February 6th the patient was transferred to the French Hospital. On admission he presented diffuse pigmentation of the skin of the whole body; he would pass for a dark-skinned Indian youth. There was no patchiness in the distribution of pigment, no areas of leucoderma, and only a few points like freckles of darker pigmentation on the face and back. Pigmentation was most marked at points of pressure, like the elbows and knuckles, and in the skin of the areolae and scrotum, which appeared almost black. The palms exhibited well-marked pigmentation, as did the nail-beds and creases about the hands, fingers, and wrists. The backs of the fingers were of darker hue than the backs of the hands. No linea nigra was distinguishable on the abdominal wall. A linear streak of lighter colour could, however, be observed on either side of the chest, running, symmetrically, from the edge of the areola about the nipple to the sternal notch. There was some rather more patchy brown pigmentation of the inner surfaces of the lips, of the inner surfaces of the cheeks opposite the teeth, and of the sides of the tongue. There was also an irregular band of intense pigmentation of the gums covering the upper and lower alveoli, leaving an unpigmented free margin and an unpigmented mucous membrane opposite the roots of the teeth. The sclerotics and subconjunctival tissue were not pigmented, but the fundi oculorum possessed a slate-grey colour such as is seen in dark-skinned races.

Beyond decrease in weight to 118 lb., a marked, rounded kyphosis, due to decubitus, muscular weakness, feeble heart sounds, and low blood pressure, there were no physical signs to be recorded. Blood pressure, 78/43; pulse, 84; temperature, 98.2° F. Radiographical examination revealed some

shadows which suggested old calcified tuberculous gland at the root of the lung, but there was no evidence of any changes in the suprarenal glands. A Mantoux test gave a marked positive reaction with vesiculation, followed by induration, which persisted for several weeks in dilution 1 in 10,000; with dilutions 1 in 100,000 and 1 in 1,000,000 the results were negative. There was a marked general reaction, the temperature rose to 103.8° F. and the pulse to 112 per minute, with headache, recovery being only completed on the fifth day. There were no symptoms pointing to a focal reaction. Laboratory investigations showed: red cells per c.mm., 6,010,000; haemoglobin, 94 per cent.; colour index, 0.78; white cells per c.mm., 6,800. Differential count gave: polymorphonuclears, 43.2 per cent.; lymphocytes, 51.2 per cent.; and eosinophils, 5.6 per cent. Meinicke reaction negative. Blood urea 40 mg. per cent. Urine normal. Blood sugar fasting, and twenty-four hours after an injection of eucortone, 72 mg. per cent.; after 50 grams dextrose half-hourly readings gave the figures 109, 83, 72, and 80. On another occasion, ninety-six hours after the last injection of eucortone, the blood sugar was 80 mg. per cent.; the boy felt weak and fainted. The blood pressure was 78/50. After the administration of eucortone, 5 c.cm. intravenously, and 50 grams of dextrose by mouth half-hourly estimations of blood sugar yielded the following results, 117, 113, 94, 68, and 78. Blood pressure readings taken at ten-minute intervals after an injection of eucortone showed no rise of blood pressure.

Progress of Case

From February 6th till March 15th, inclusive, the patient received 5 c.cm. eucortone intravenously each day, with the exception of the ninety-six hours above-mentioned. Under this treatment he remained free of most of his symptoms, such as vomiting, insomnia, anorexia; but there was only a gain of 2 lb. in weight. There was but slight lessening of pigmentation, and the blood pressure varied between 70/50 and 78/50. On March 1st three horizontal lineae atrophicae had appeared on either side of the spine opposite the eighth and ninth dorsal spinous processes. Lines of lighter colour, like those already mentioned above, had appeared, two on each side, symmetrically placed along the pectoral margin of the axilla, and one running from the sternal notch towards the umbilicus.

On March 16th whole-gland suprarenal (Armour) was substituted for the eucortone; three tablets, each of 2 grains dried gland (= 10 grains fresh gland), were given by mouth thrice daily. Within two days the patient expressed himself as feeling much better and stronger than he had done for many weeks. In the following ten days he gained 3 lb. in weight and the blood pressure rose to 90/55.

On March 31st whole-gland suprarenal was replaced by a special extract of cortex prepared by Allen and Hanburys for oral administration. It was given in doses as suggested, but the gland equivalent was unknown to me at the time. Within twenty-four hours the lad said he did not feel so well, his appetite began to fail, there was immediate loss of weight, and the blood pressure fell to 78/48. It was then found that this liquid extract, which was being given in doses of half an ounce thrice daily by mouth, only contained 1 gram of cortex per 3 c.cm. It also contained 0.05 per cent. adrenaline. A return to whole gland by mouth was made on April 5th, with immediate benefit; all previous symptoms disappeared, the blood pressure rose to 88/58 in forty-eight hours, weight increased, and appetite was excellent. During the ensuing two weeks improvement was rapid; he was able to walk several miles, muscular power was good; to exercises directed to correct the kyphosis he responded well. The pigmentation was diminishing very considerably, and the blood pressure remained higher than previously. The pulse sounds noted during sphygmomanometrical readings appeared almost normal. About the middle of April it was noticed that the breasts were enlarged, resembling those of a girl a year before puberty, but without changes in the nipples. During forty-eight hours, April 18th to 20th, treatment was discontinued, with no obvious ill effect.

On April 21st cortin organon, 5 c.cm. by mouth, was given. By the evening of that day symptoms of suprarenal insufficiency developed. These had not been noticed during the previous two days, when treatment had been withheld. After

three days on 5 c.cm. by mouth, 5 c.cm. were given twice daily intramuscularly, with some improvement. Cortin is a preparation of suprarenal cortex made at Oss in Holland by N. V. Organon, who very kindly sent me a supply for a trial at the instance of Dr. Alison Macbeth: 1 c.cm. represents 50 grams of fresh gland. The dose advised—namely, 5 c.cm., intravenously—for maintenance is doubtless about correct, and corresponds fairly closely to that of eucortone.

A second return was made to dried whole gland, and the patient took his discharge from hospital on May 4th, 1933, with a supply of tablets. He came up once two weeks later for more tablets, and then disappeared; all efforts to trace him failed. On July 1st, 1933, he returned in a condition of collapse, with all his previous symptoms returned. Weight, 119 lb.; temperature, 98° to 99° F.; pulse 72/84; blood pressure, 60/36. There were present extreme asthenia, negativism, nausea, vomiting, and abdominal pain. During the first week, 10 c.cm. eucortone was given daily; later an oral preparation of eucortone, made by Allen and Hanburys, was tried, and the addition of adrenaline subcutaneously was made. The patient continued to lose weight, and it was impossible to get him to take nourishment. A return was made to intravenous eucortone, kindly provided by Allen and Hanburys: 10 c.cm. were given twice on the first day (July 22nd) and the second day, then 10 and 5 c.cm., and thereafter 5 and 5 c.cm. each day. There was some response in that a little nourishment was taken and the extreme sense of weakness was less marked; the blood pressure remained at 60/36. Eucortone was then discontinued, as the supply had come to an end. Twenty-four hours later the patient collapsed, became comatose, and died. Necropsy was refused.

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TREATMENT AND CONTROL OF ESSENTIAL HYPERTENSION

A NEW THERAPEUTIC MEASURE

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In 1917 Cyriax¹ reported good results in cases of moderately high blood pressure obtained by what he described as "mobilization of the spinal column," by which he meant active and passive movements of the vertebral joints, and passive manipulations, vibrations, pétrissage, etc., of the erector spinae muscles. His explanation of raised pressure was, apparently, that congestion of these parts led to irritative states of the erector spinae, setting up a series of sensory stimuli to the posterior spinal nerves, which in turn gave rise to a series of pressor effects. Whatever the explanation, his figures seemed to show a definite diminution of the blood pressure in his patients.

Although unwilling to accept the theory on which the treatment was based, I ventured to modify his method by substituting electrical stimulation of the skeletal muscles, and submitting patients with high grades of pressure to treatment on these lines. As a preliminary the patients were tested to see what effect the resulting muscular contractions had on the pulse rate, particularly as some of them were on the verge of cardiac failure, a few actually exhibiting oedema of the ankles and a more than moderate enlargement of the heart. In every case the pulse rate dropped, sometimes by eight beats to the minute; in a