ADDICTION TO ENDOCRINE GLAND EXTRACTS*

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In bringing forward this subject I found some difficulty in selecting a suitable short title. The term *misuse* would involve far-reaching excursions into debatable regions of medical practice. The word *abuse* is also a wide one, and includes the legitimate denunciation of the use of thyroid for slimming, and of the use of "monkey gland" for the rehabilitation of exhausted roués. Although both of these will be mentioned again, it is with another aspect of the subject that I intend to deal primarily in discussing cases of *addiction* to endocrine glands and extracts. The suitability of the term "addiction" will be considered later.

The endocrine glands have been called the regulators of metabolism. Cannon¹ (1922) points out that they have functions other than that: they regulate growth; they determine the development of intelligence; they fix the appearance of the secondary sexual characteristics and the regular sequences in reproduction; and they control the nature and rate of the chemical changes which take place in the body. There is no question of the importance of the endocrine glands and of their capacity to cause profound disturbances in the above-mentioned processes. The functions of all of them are closely interrelated, but the manner of these interrelationships is very imperfectly understood. It is only fair to ourselves and to a satisfactory development of the knowledge of their activities that we recognize the present limitations of our ability to control these "controllers," and to see clearly the dangers of using careless methods and of making hasty inferences. In our present state of knowledge indiscriminate pluri-glandular therapy is not likely to be satisfactory.

Thyroid Gland

More is known about the thyroid than about any of the other endocrine glands. There are syndromes associated clinically with over- or under-activity of the thyroid which can be closely paralleled artificially through thyroid feeding in the one case or thyroidectomy in the other. Further, in the case of the thyroid a substance has been isolated in pure chemical form which is the active principle of the gland (thyroxine, Kendall). The most conspicuous function of the thyroid is the regulation of the rate of oxidation and energy transformation in the living cells of the body. Overactivity of the thyroid is manifested by increased rate of combustion; underfunction by decrease. There is a legitimate use for thyroid therapy in conditions of hypothyroidism, including some forms of goitre, and in myxoedema and cretinism. It is a problem whether thyroid therapy is ever indicated in conditions which are not clearly those of hypothyroidism. It has been stated: "The diseases in which thyroid has been given include nearly all the chronic and many of the acute troubles known to humanity; in some of them it has seemed to benefit; in most it has proved useless."

A further problem is whether it is legitimate to use thyroid in the treatment of obesity. It is probable that it may be used with benefit if combined with restricted diet. The effect of prolonged undernutrition is to reduce the rate of metabolism; that of giving thyroid is to raise it and so help the loss of tissue. But the indiscriminate use of thyroid for weight reduction and self-dosing by the laity may be extremely dangerous. Yet the use of

thyroid without a physician's advice in order to reduce weight is quite common.

Cases showing Ill Effects

In the classical case of von Notthafft² (1898) a man took 1,000 thyroid tablets in five weeks to reduce his weight; he lost 30 lb. in that time. At the end of the third week the neck became swollen and an irritable cough started. Then followed palpitation, insomnia, severe tremor, and exophthalmos, and at the end of the fifth week great thirst and glycosuria.

Means³ (1922) quotes data regarding the use of thyroid by the pupils in a girls' boarding school in Massachusetts. The craze among the girls was to be thin and have lithe figures. Many of the girls became severely ill.

Symptoms of hyperthyroidism following thyroid medication in obesity are also recorded by E. Mosler⁴ (1924), who quotes six cases of damage from thyroid medication by lipolysin, thyraden, and other thyroid preparations, and by Franke⁵ (1925), who has seen four severe cases following the use of lipolysin tablets for reduction. Mosler comments on the risks of cures taken in sanatoria where rapid loss of weight is made, and urges that lipolysin and all other thyroid preparations should be taken only under the prescription of a physician, and their use closely supervised.

Parkins⁶ (1929) records the case of a woman patient aged 45, who four years before had had thyroid extract prescribed by her doctor to reduce weight. She had gone on taking it and had taken 11,805 grains in four years, an average of 8 grains of thyroid extract (B. W. and Co.) a day. She was found to be suffering from heart failure and acute pulmonary oedema.

Hyperthyroidism may follow thyroid medication in simple goitre.

Elliot⁷ (1907) described a well-developed thyroid toxæmia of a few weeks' standing in a young man of 22 years, who had had a small simple goitre from childhood. Four months before he had been induced to take thyroid to remove his goitre, and, not observing any effect on the tumour, had gradually and steadily increased the dosage, believing the stuff to be harmless. From 15 grains daily—the initial dose—he had attained an average of 75 grains a day, and he asserted that he had taken 200 5-grain tablets during the preceding week. The maximum daily quantity was 150 grains. He had gained perceptibly in weight. Discontinuance of the drug led to prompt subsidence and final disappearance of toxic symptoms.

While hypothyroidism may be successfully treated by supplemental thyroid feeding for prolonged periods—Hardenbergh⁸ (1920) quotes a case so treated for twenty years—ignorance or lack of supervision may bring about symptoms of hyperthyroidism. Sir William Hale-White permits me to quote one of his private cases.

"One filthy night—rain and wind—I was called out of town about twenty-five miles after dinner to see an elderly lady said to be very ill. I found this was so. She was the first patient for whom Ord had prescribed thyroid for myxoedema. It did her so much good that she came to regard it as her special tonic, and whenever she felt run down she increased her dose, so that when I saw her she was obviously dangerously ill from thyroid poisoning, which was quite unsuspected by her doctor, who did not know that she was taking it. By good luck I got the correct history; then I saw the tablets, and, needless to say, she got perfectly well, although had matters gone on as they were she must have died."

F. Müller⁹ (1927) describes a case in a myxoedematous child following administration of fresh thyroid gland. The mother, in her anxiety for her child's development, went to the slaughterhouse and obtained fresh gland daily as the animals were killed. The child had the usual signs of hyperthyroidism—palpitation and tachycardia, tremor, restlessness, raised temperature, alimentary glycosuria, digestive disturbances, and looseness of the bowels.

From personal communications of doctors I have learned of two patients who produced symptoms of intoxication from taking thyroid under a misapprehension of the nature of their

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complaint (Patterson,¹⁰ 1934). One of the earliest cases of this kind was that of a medical student who dosed himself for exfoliative dermatitis, and developed acute mental symptoms and signs of Graves's disease (but not exophthalmos), lasting several weeks after thyroid was stopped (Boinet,¹¹ 1899).

We have seen that thyroid intoxication may be produced by patients through ignorance, stupidity, or from motives of vanity, but there is another psychological factor which I have described¹⁰ (1934). The effect of thyroid extract is to speed up the metabolism and rate of energy transformation in the body, and it is understandable that there should be a certain tonic effect or increased feeling of well-being. This appeared to be the factor influencing my three patients, who produced toxic symptoms by overdosage.

Rare Symptoms

The usual symptoms of hyperthyroidism have been described already. I may add a few notes on the less usual symptoms which have been recorded. In a few cases exophthalmos has been produced by thyroid medication. E. Möller¹² (1930) has collected eight cases from the literature, and he adds one of his own. Bergstrand¹³ (1932), in reporting the post-mortem examination of a fatal case, states that of the eight cases cited in the literature of acute Basedow's disease after treatment with thyroid, three had originally suffered from myxoedema. Moorhead¹⁴ (1931) reports a similar case of a myxoedematous woman who took up to 12½ grains a day of thyroid extract for three years. She developed unilateral exophthalmos as well as the usual symptoms of thyroid intoxication, tachycardia, palpitation, extreme nervousness and restlessness, insomnia, and loss of weight. In the patient I have described,¹⁰ who took large doses of thyroïdin at intervals, intense desire to micturate every few minutes and to attempt to evacuate the bowels two or three times every hour was brought about. In another woman with thyroid addiction I observed that auricular fibrillation and congestive heart failure followed bouts of taking thyroid.

Hyman¹⁵ (1930) describes a case of a man aged 49 with osteo-arthritis and a basal metabolic rate of -28 per cent., who was given thyroid, and later thyroxine, and who developed paroxysmal tachycardia. Standish¹⁶ (1916) quotes eight cases from the literature and adds three of his own of retrobulbar neuritis with central scotoma, which are attributed to the use of thyroid extracts. Birch-Hirschfeld and Inouye¹⁷ (1905) found in experiments on dogs that anatomical changes—a degeneration of ganglion cells of the retina, with secondary degeneration of the optic nerve fibres—resulted from thyroïdin.

Patients with pluriglandular syndrome and scleroderma appear to be very susceptible to thyroid products. Sinton and Mamon¹⁸ (1927) report a case in which injections of small doses of thyroxine (in all 6 milligrams in divided doses) produced violent signs of hyperthyroidism.

Adrenal Extracts

When Kaplan¹⁹ (1905) introduced the "hypodermatic" use of adrenaline chloride in the treatment of asthmatic attacks, he recommended doses of 0.3 to 0.6 c.cm. (5 to 10 minims) or more, and said these were harmless. Patients have been described who have taken 15 drops three or four times a day for five years, sometimes as many as thirty injections a day, and without by-effects. Duke²⁰ (1928) has had a patient who took 4 ounces in twenty-four hours, 2 c.cm. in a dose, every fifteen minutes for prolonged periods of time. Some patients show a remarkable tolerance to adrenaline injections.

Etienne, Richard, and Claude²¹ (1926) report a patient who took in two years over 2,000 milligrams of adrenaline

without appreciable change in the cardiovascular condition. His hypertensive asthma was much benefited by the treatment. Ricaldoni²² (1925) has seen a patient who took a daily dose of 6 milligrams for ten years, and then for three years 9 to 12 milligrams; he had 31,000 injections, each of 1 milligram, in thirteen years. His condition Ricaldoni describes as a form of adrenalinomania, kept up not only by the asthma, but by the fear of an attack. His blood pressure remained 120/70, and his heart was only slightly enlarged. In such patients the dose can often be reduced greatly. In any chronic illness it is necessary to be careful; 10, 12, or 15 minims are often given when 2 to 4 minims would be enough.

Duke²⁰ found 10 to 15 grains of aspirin in whisky to be a substitute, recommending this as much less dangerous than morphine; he gave enough whisky to make the patient lie down and go to sleep, and that was usually the end of the attack.

Lamson²³ (1929) describes three cases of epinephrine addiction in bronchial asthma, in which psychotherapy and the use of a placebo produced a cure.

An asthmatic may develop the habit of taking large amounts of adrenaline at frequent intervals, even though he claims little relief from the drug; the periodicity of injections is often striking. Also, relatively small doses may be effective if given by the physician, but larger ones administered by the patient or by one of his family may fail to give relief. The earlier writers recognized and possibly overemphasized the neurotic element in bronchial asthma. In more recent times this phase of the problem has too often been neglected in favour of specific hypersensitive phenomena. Psychic factors may be largely responsible for the habitual use of adrenaline.

Hoxie and Morris²⁴ (1920) describe a case of chronic adrenalism in a married woman of 24. For six years she had had continuous asthma throughout the year, aggravated by lying down and worse after eggs, pears, peaches, and other fruits. Since the onset she had been using adrenaline, about 7 c.cm. daily; she was also addicted for a time to inhalations of chloroform. Up till a year before she was also a user of morphine, in amounts not known. All these habits were formed in attempts to relieve the constant dyspnoea. Whenever deprived of adrenaline she became frantic, and if allowed to go on would develop cyanosis of lips and fingers, with loss of radial pulse, and blood pressure readings of 155/140. After adrenaline the dyspnoea would subside and the blood pressure become 160/98. The skin was scarred by hypodermics. The patient died suddenly two and a half hours after injection of 1 c.cm. of adrenaline. Adrenaline and a hypodermic outfit were found concealed in the ward. The post-mortem examination showed mild pleural adhesions, collapsed right lung, enlarged heart with sclerosed coronary vessels, and atheroma of the aorta.

A somewhat similar case is described by Laignel-Lavastine and Bernal²⁵ (1930)—that of an asthmatic who, when deprived of his injection, committed suicide. The injection in this instance was evatmine, in which adrenaline is mixed with extract of whole pituitary gland. The patient, whose asthma was of twenty-seven years' standing, was accustomed to taking six or seven ampoules of evatmine a day with relief, but later required three ampoules at each injection. Substitution by morphine was tried, but the patient took his life by hanging himself in the hospital ward. In the discussion on this case one patient was quoted who had kept a record of his treatment, and had taken 2,000 ampoules of evatmine without forming a habit. Apart from attacks, he had no desire for the drug; and in an attack the evatmine acted as well as ever.

Flandin²⁶ quoted a patient who had become accustomed to giving himself 200 to 240 injections in the twenty-four hours of the serum of Heckel, which contains adrenaline. The fear of an attack was enough to call for the injection; and the need for injection survived the cure of the asthma.

Sajous states that the prolonged use of adrenal preparations may induce chronic adrenalinism with severe cardiac disorders, especially of the myocardium, dyspnoea after slight exertion, tachycardia, raised blood pressure, polyuria, icteric staining of the conjunctivae, and increase in weight.

Moure²⁷ (1928) comments on the dangers of subcutaneous injections of adrenaline, and describes cases of large sloughing wounds on the external surface of the thighs, which required extensive skin grafting.

Hautefeuille and Rinuy²⁸ (1933) have seen gas gangrene and death after seven injections into the thigh for bronchial asthma of 5 c.cm. a day of the serum of Heckel.

Adrenaline preparations are very useful in the treatment of asthma. The dose required may often be small and yet efficacious. Physicians should be aware of the psychological state and often neurotic condition of their patients; they should supervise and keep control of the treatment, and instruct their patients in cleanliness in the technique of injection.

Use of Other Extracts

Since the introduction of insulin for substitution therapy in diabetes, a new outlook has been opened up for diabetics, and strict dieting is no longer a necessity in order to keep them alive. The increased dietary allowed to the diabetic when it is balanced by sufficient insulin may lead to abuse, but no great proportion of cases of this nature is met with. Indeed,

"the difference is too nice,
"Where ends the virtue and begins the vice."

In the case of the gonads the psychological repercussions have been noted in the literature of the world from the earliest times. The desire to regain youth has always been a favourite wish of mankind. The attempts that have been made to bring this about by Steinach, and especially by Voronoff's method of grafting glands* from the chimpanzee or baboon, have brought only a transitory increase of vitality (Zondek,²⁹ 1935). But the knowledge of failure or lack of manly or womanly potentiality may have far-reaching psychological effects; the *amour propre* is wounded, and defensive habits may be formed, as in the following case:

A woman of 33 had had, at the age of 21, one ovary and most of the other removed for cystic disease. The operation was followed by aplastic peritonitis from low-grade infection, and two operations were later carried out to relieve adhesions. The patient's abdominal symptoms subsided. Menstruation, however, became irregular after the ovarian operation, and two or three years later ceased. She suffered considerably from nervous depression, and for many years had weekly injections of an ovarian extract. This she was accustomed to give herself; she was miserable without it, and said she was always better after it. Substitution by other newer, and presumably more potent (because standardized) ovarian extracts was stated by the patient to have no useful effect. She has been under observation now for eight years, and insists on giving herself her weekly injection of the one extract. She has not increased the dose, nor has she shown any tendency to use other drugs. In other respects she is a normal person.

Nomenclature

Though most of the cases of the misuse of endocrine gland extracts which I have quoted are properly an "abuse," some are comparable in their psychological content with instances of overmastery by morphine, heroin, and alcohol, for which the term "addiction" is used.

Though "addict" was used first in 1909 for one who is addicted to the habitual and excessive use of a drug or the like, the word is derived from a very old source. Addicted in Roman law meant delivered over judicially or devoted; hence was derived the sense of being attached by one's own act to a person; hence self-addicted to ("addicted to a melancholy," *Twelfth Night*, II, v, 22; "addicted to wine or strong drink," T. Taylor (1576-1633)). The noun "addiction" therefore meant in Roman law a formal giving over by sentence of a court, hence a dedication to a master; and the use

of the word in the sense of the state of being (self-) addicted to, dates from 1641 (*N.E.D.*)—for example, "addicted to tobacco" (Johnson). In his address to this society in April last on definitions of addiction, Dr. E. W. Adams³⁰ clearly stated the characteristics of these masterful drugs.

In cases I have quoted in regard to both thyroid and adrenal preparations, these have produced a tonic effect or state of euphoria, a craving and an uncontrollable tendency to revert to the drug after an apparently successful withdrawal. The term "addiction" is, however, not wholly suitable, though most people know what is meant. Nor is the word "habit" satisfactory. Applied to drugs and alcohol, the association of the term is with a bad habit. Thyroid-taking may be necessary in cases of hypothyroidism; its use in excess may be a bad habit but another word is needed to express the psychological condition in some of these cases. French medical writers use the term "manie," and by attaching it to the drug or substance in question produce a compound word, as *thyroidinmanie*, *evatminmanie*. This is a suitable way of describing the manias of habitual indulgence in certain drugs. Serejski³¹ (1928), professor of therapeutics in Moscow, used the term *sucht* (desire). Of his three cases of *thyroidinsucht*, two were cases of hypothyroidism which had been benefited by taking thyreoidin, and who stole and surreptitiously took it to excess for its tonic effect.

The third, which he labels as *pseudosucht*, was an undeveloped youth of 18, who in his desire to grow had taken so much thyreoidin that he had lost count, but he had spent 300 roubles in five months, and had had 180 pituitrin injections—two ampoules a day. The patient noted that he gained but did not lose weight. He was told of the risk to his health, but said if he did not grow his life was no use to him. He later developed schizophrenia simplex.

The word "desire" may be a good one, but Serejski's instances are not like those I am specially dealing with. It would seem that "addiction" is suitable unless we adopt the French term "manie." "Manie" is a useful general term. There are certain cases in which it is not so much the drug as the needle puncture which is the predominant factor, with some psychological element of self-torture or submission to others (masochism). Morel-Lavallée has suggested the term "kentomanie" for these cases.

Summary

In this brief review of the literature a series of cases has been collected of abuse of endocrine gland preparations; in some a habit has been formed comparable with addiction to other masterful drugs. I have pointed out some of the dangers that may follow the injudicious use of thyroid, adrenal, pituitary, and other extracts. It is probably necessary in cases of asthma to hand over a hypodermic syringe and solutions of adrenaline to the patient or to a relative, since the remedy is to be injected at the onset of an attack.

Whenever thyroid is prescribed, especially in conditions other than hypothyroidism, it should be used with the greatest care. Self-dosing with thyroid is highly undesirable. The profession should do its utmost to discourage this practice. In the matter of placing these preparations under the control of the Dangerous Drugs Act there are many difficulties. The husband of one of our patients, a man prominent in public affairs, impressed with the dangers of thyroid gland preparations, made a move with this object; he did not succeed.

It is the duty of medical men prescribing these drugs to exercise proper supervision and control of their use by patients. They should be aware of the possible dangers, and should warn their patients, keeping them under careful observation, so that the drug may be stopped at once if ill effects arise.

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ESSENTIAL PURPURA HAEMORRHAGICA *

BY

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Cases of purpura have been reported from the earliest times, and a recent writer has even quoted instances in the Bible. No doubt scurvy and purpura have sometimes been mixed up, but it is evident that definite cases of purpura haemorrhagica occurred thousands of years ago.

In modern times the first to describe the clinical symptoms of purpura was Paul Werlhof (1699-1767), a German physician, who wrote of it in 1735 as "morbus maculosus," as stated by Professor I. Abt.¹ Johan L. Schönlein, born in 1793, described peliosis rheumatica, while another distinguished physician, Edward H. Hensch (1820-1910), described purpuric symptoms accompanied by pain in the abdomen, vomiting, fever, and the passage of blood in the stools. He was aware that in some instances it was associated with rheumatic pain and swelling. The names of Donne, Schultze, Sir William Osler, and Bizzozero are noted in the literature; and Georges Hayem described the platelets, which he stated were much concerned with clotting of the blood. It was in 1889 that Denys recorded that the blood platelets were diminished in purpura haemorrhagica. W. W. Duke of Johns Hopkins University was the first to describe the prolongation of the bleeding time in the disease. E. Glanzmann (University of Berne) was of opinion that the Schönlein and Hensch types of purpura were anaphylactoid. E. Frank (University of Breslau) described the disease as essential thrombopenia. He was of opinion that purpura could not occur without some damage to, or increased porosity of, the capillaries. Finally, great credit is due to Paul Kaznelson, who in 1916 was the first to suggest splenectomy for purpura haemorrhagica, and certainly there have been some brilliant results from this operation when performed in suitable cases.

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¹ *Amer. Journ. Dis. Child.*, February, 1935.

Varieties of Purpura.—Purpura is usually divided into (a) primary, and (b) secondary. Examples of the secondary type are certain blood diseases such as leukaemia, pernicious anaemia, and aplastic anaemia; haemolytic jaundice, Gaucher's disease, carcinomatosis of the bone marrow; infections such as cerebro-spinal fever; and the type following the use of chemical substances such as iodine, benzol, etc. The primary form can be subdivided into (1) haemorrhagic purpura (purpura simplex, purpura haemorrhagica, and purpura fulminans), and (2) anaphylactoid purpura (Henoch's and Schönlein's purpura). It seems certain that some of the cases of anaphylactoid purpura, and also a number of cases designated as haemorrhagic purpura, are by no means all primary, and future investigation will demonstrate which cases are really primary.

Essential Purpura Haemorrhagica

In this type, in addition to the purpuric spots present in the skin and mucous membrane, there is also bleeding from one or more areas of mucous membranes, such as the nose, gums, mouth, uterus, urinary tract, intestinal tract, stomach, etc. The haemorrhages may be accompanied by anaemia, which is sometimes severe. Occasionally a raised temperature is present. The general condition of the patient may be stated to vary in accordance with the loss of blood.

In my experience *the spleen is not enlarged* in these cases either clinically or as seen at operation or after examination by the pathologist. Of course there may be cases in which the spleen is enlarged temporarily. Certain tests are invaluable in the elucidation of this type—thus the presence of *thrombocytopenia* (the platelets being reduced from the normal figure of about two to three hundred thousand to forty thousand or less, and sometimes no platelets being seen at all for a time; *increased bleeding time* (from what is usually accepted as normal—namely, three to four minutes) up to twenty to thirty minutes or even ninety minutes or more in rare cases; a *positive capillary resistance test* (estimated by placing a rubber bandage or the armlet of a blood pressure instrument around the upper arm and keeping the pressure midway between the systolic and diastolic for three minutes, when, if positive, haemorrhagic areas appear between the wrist and the lower end of the bandage). There is also described a *flat-topped blood clot*, but this cannot be looked upon as diagnostic, for it is present in a number of other complaints. The blood coagulation is practically normal, in marked contrast with haemophilia.

Acute, chronic, and intermittent forms of essential purpura haemorrhagica are described. The disease should always be looked upon as a serious malady, for a case which may not appear to endanger the life of the individual may terminate with tragic suddenness.

Two Case Reports

I have had five typical cases of essential purpura haemorrhagica, all of which have been cured by splenectomy. The notes of two, both of which were operated on nine and a half years ago, are recorded below.

CASE I

Winnie B., aged 10 years, was admitted to the Royal Waterloo Hospital on 12/7/25. She was bleeding from the gums and nose, and a number of purpuric spots were present on the body and also some bruises. During the previous year she had attended the hospital for purpura as an out-patient.

Examination.—The patient was suffering from continuous oozing from the gums, which did not respond to any treatment. The temperature was 98.6° F., pulse 106, and respirations 24. Nothing abnormal was observed in the heart, lungs, or abdomen. The tonsils were enlarged. She was subject to