MODERN ENDOCRINOLOGY AND MENTAL DISORDER.*

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THERE are in the wards of every mental hospital numbers of persons who for long periods of time exhibit profound disorders of emotion. Thus, we note the fixed depression of the melancholic, the boisterous exuberance of the manic, and the mechanical indifference of the primary dement.

In each of these three types of mental disorder the disturbance of affect dominates the clinical picture and, indeed, may be the one and only symptom of the disease. Some of the worst cases of melancholia have no delusions, and many cases of mania and dementia præcox present little disorder of intellect. Although there are a number of psychological theories which partially explain such mental states, and it is admitted that the latter are often precipitated by psychological factors, nevertheless, once those who suffer from them have reached the stage of certification, they are no longer amenable to psychotherapy, except in a very broad sense. Moreover, in both dementia præcox and manic-depressive insanity there are strong reasons for suspecting the existence of a constitutional defect, which renders the individual peculiarly susceptible to emotional disturbance. Attacks of mania and melancholia tend to occur in cycles, and in some instances it is impossible to find a provoking cause. Again, in dementia præcox the lack of affect and the withdrawal from reality often seem to depend more on a primary failure of instinctive driving force than on unfavourable circumstances in the patient's environment. A man whose instincts are of normal strength probably finds little difficulty in outgrowing the stage of infantile fixation through which apparently we all must pass. At all events, whether these mental illnesses are primarily psychological or physical in origin, there is no doubt that when fully established they present abundant material for study from a physical standpoint. In this connection two questions present themselves: Firstly, what is the nature of the organic processes which parallel such disturbances of instinct and emotion? And secondly, is it possible to modify or alter these organic processes by any form of medication?

ORGANIC BASIS OF INSTINCT.

William James (1) maintained that the essential nature of all emotional consciousness consisted of sensations arising from change in the internal organs

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of the body. He considered that organic sensation was the basis of all emotion, and he held that if a man were to become corporeally anæsthetic, he would be " excluded from the life of the affections, harsh and tender alike, and drag out an existence of merely cognitive or intellectual form ". According to this theory, the impulses arising from the muscles, skin and internal organs constitute the very essence of emotional experience, and if these physiological manifestations are abstracted, nothing of the emotion remains. The actor feels anger and fear because he assumes the attitudes by which such emotional states are expressed: " Sit all day in a moping posture, sigh and reply to everything with a dismal voice, and your melancholy lingers." James, however, overlooked the fact that, although two things may be invariably associated with each other, they are not necessarily identical. As Stout (2), in his criticism, very aptly remarks: " A stone cannot fall into the water without making ripples, but the ripples are not the stone." Organic sensation may be a factor in the constitution of emotional states, but it is not the sole factor.

James's theory of the emotions has been excellently reviewed in the light of modern discovery by Cannon (3), and it is proposed to quote at some length from the latter's work. After calling attention to Sherrington's experiments, in which the emotional behaviour of dogs remained unchanged after the spinal cord and both vagi nerves had been divided, he describes how cats who had had their entire sympathetic nervous system removed continued to show all the superficial signs of rage in the presence of a barking dog, despite the absence of all afferent impulses from the viscera. He further points out that in certain emotions, such as fear and rage, there is evidence of profound sympathetic stimulation characterized by the following reactions, viz., acceleration of the heart, contraction of arterioles, dilation of bronchioles, increase of blood sugar, inhibition of activity of digestive glands, inhibition of gastro-intestinal peristalsis, sweating, discharge of adrenaline, widening of pupils and erection of hairs. These reactions, however, occur not only in emotions such as fear and rage, but also after exposure to cold and during fever, so that, according to James's theory, exposure to cold and fever should *feel* the same as the emotions of fear and rage. This, of course, is not the case. Cannon was able to produce artificially visceral changes typical of strong emotion by injecting adrenaline into students, but the latter failed to experience any specific emotion as a consequence of such medication. In finally rejecting James's theory of emotion, he says that, although the processes going on in the thoracic and abdominal organs in consequence of sympathetic (emotional) activity are truly remarkable and various, their value to the organism " is not to add richness and flavour to experience, but rather to adapt the internal economy so that in spite of shifts of outer circumstance the even tenor of the inner life will not be profoundly disturbed ".

Cannon considers that the thalamus is the region in which resides the

neural organization for the different emotions, and that thalamic processes are the source of affective experience. He refers to Head's cases of unilateral lesions in the thalamic region, in which there was a marked tendency to react excessively to affective stimuli on the damaged side of the body. Head attributed this extravagant influence of affective stimuli, whether from surface receptors or from memories, to release of the thalamus from cortical inhibition, and the theory now generally held is that the diencephalon is the nervous structure concerned with the experience of emotion, and that its activities are held in constant check by the cerebral cortex, except as occasion for emotional expression arises.

Since, then, the thalamus is the seat of emotional experience, it follows that in cases of pathological persistence of affect, such as mania and melancholia, this region of the brain must in some way be implicated. At all events, whatever neural combinations underlie such affective states must remain in operation for long periods of time, and exclude all other reactive patterns. Doubtless, however, this derangement of the diencephalon is purely functional in nature, for how, otherwise, could such cases recover, as many of them in fact do? Applying the thalamic hypothesis to dementia præcox, where complete apathy is the rule, we may postulate here a temporary or permanent side-tracking of the thalamus from other cerebral processes, as a result of which the patient becomes more or less isolated from affective life. It is as though stimuli from within and without the organism were passing to and from the cerebral cortex without making contact with the thalamus, and, indeed, many such patients respond to an unpleasant sensory stimulus, such as a pinprick, with just that absence of feeling tone which is held to be added to simple sensation by thalamic participation. Affective experience, however, is only one aspect of instinctive life, and the conative forces which are so closely associated with emotion are of just as much importance to the organism. Affective states would indeed be of little use if they were unable to fan the flame of desire and stimulate achievement. Our efforts to view emotions from the physiological level must, therefore, include an attempt to correlate the executive side of instinct with organic processes.

Cannon (4) has shown that emotions such as fear and rage involve profound stimulation of the sympathetic nervous system, and an increased secretion of adrenaline by the suprarenal glands. The adrenaline co-operates with the sympathetic nerve impulses in calling forth stored carbohydrate from the liver, and in effecting a suitable distribution of blood to various organs of the body. It further has the effect of abolishing muscular fatigue, of securing relaxation of the bronchial tubes, and of rendering the blood more rapidly coagulable. These adreno-sympathetic activities are interpreted by Cannon as attempts at biological adaptations to conditions in wild life. Thus, the circulation is flooded with sugar in anticipation of increased muscular activity in fighting or flight; the blood is taken from the abdomen and distributed in

the heart, lungs, central nervous system and limbs, where it would be most required in an external emergency; the bronchial tubes are relaxed to permit a greater intake of air, and the blood is rendered more coagulable, so that less would be lost in case of injury. All these reactions are protective in nature, and ensure that the line of conduct, which has been prompted by the emotion in question, will be executed with the greatest degree of safety to the individual. Here we have an example of an endocrine secretion participating directly in an emotional reaction, and preparing the organism for subsequent behaviour. Moreover, since the reactions induced by the adrenaline are purposive in character, they represent to some extent the organic basis of conation. While Cannon deals principally with the instinct of self-preservation, it is almost certain that all the other instincts are similarly implemented by endocrine activity—a supposition which is supported by the close anatomical proximity of the diencephalon and pituitary gland. For this reason it is imperative that all who are interested in the treatment of mental disorder should keep in close touch with modern developments in endocrinology, and seek to apply its principles to their patients. It is now proposed to mention certain of these discoveries and to give a brief account of an attempt to utilize them in the field of therapeutics.

Modern Endocrinology.

The science of endocrinology is now so complicated and its literature so vast and ever-changing, that it is very difficult for one man to keep in touch with all its ramifications. The subject has been excellently reviewed in Cameron's recent book (5), and readers should consult this, or larger works, for full information on the various points referred to here.

While it has long been known that the disease called acromegaly is associated with tumours of the anterior lobe of the pituitary, Evans and Simpson (6) were the first to produce growth effects in animals by injecting them with extracts of the gland. They demonstrated that young rats which were receiving such treatment grew at an abnormal rate, and eventually far outstripped the control animals. Since it has also been shown that hypophysectomy arrests growth in immature animals, the existence of a growth hormone in the anterior pituitary gland would appear to be definitely established. About eight years ago, however, Zondek and Ascheim (7) and P. E. Smith (8) secured a totally different effect by implanting anterior pituitary gland in young animals. By such a procedure they were able to induce precocious sexual maturity in rats and mice, as shown not only by premature mating, but also by the production of certain striking changes in the ovary and uterus. The ovaries of the treated animals were much larger than those of the controls, contained an increased number of follicles, and exhibited abundant evidence of ovulation, despite the fact that the normal age of sexual maturity had not been attained. The uteri corresponded in size and development to those of adult animals—a

phenomenon which was subsequently found to be due to the action of a further hormone, viz., œstrin, secreted by the stimulated follicles of the ovary. Smith and Engle (9) obtained corresponding gonadotropic effects in male animals by means of treatment with anterior pituitary extracts. The injections resulted in an increased growth of all the tissues of the testicle, including the interstitial cells, and enlargement of the penis and sexual apparatus. Here again, however, the enlargement of the accessory sex organs was found to be due to the action of an additional internal secretion elaborated by the interstitial cells of the testis, and not to the direct effect of the pituitary extract. Premature spermatogenesis has never been produced in immature animals, and on the whole the male gonads show a more variable response to pituitary hormone than do those of the female.

There is yet a third hormone formed by the anterior lobe of the pituitary gland which is claiming much attention at present. After the operation of hypophysectomy in animals the thyroid gland shows signs of atrophy, and evidence of its functional activity diminishes. Conversely, the injection of potent extracts of anterior pituitary is followed by parenchymal hypertrophy of the thyroid gland, and an increase in the oxygen consumption of the body. Friedgood (10) studied the basal metabolic rate and the pathology of the thyroid gland in 30 guinea-pigs injected with anterior pituitary extracts over a period extending from 48 hours to 190 days. He found that there was an initial rise in the basal metabolic rate as a result of the injections, but that, if the latter were continued for any length of time, a spontaneous remission occurred. Parenchymal hypertrophy and hyperplasia of the thyroid gland appeared simultaneously with the systemic evidence of hyperactivity, but showed a tendency to recede in spite of continued injections of the extract. Spence (11) also has demonstrated the stimulative effects of anterior pituitary extracts on the thyroid gland, and the subsequent regression of the gland under conditions of prolonged medication. He further noted a definite increase in the size of the suprarenal cortex in the experimental animals. The possibility of the development of " anti-thyroid " or " anti-pituitary " substances in the blood, which would account for the above-mentioned failure to maintain a high basal metabolic rate in spite of continued medication, is at present under investigation.

That the anterior pituitary gland secretes three hormones which stimulate growth, the sex organs and the thyroid gland respectively is, therefore, definitely proved, and there are good reasons for believing that the development of the suprarenal cortex is also under its influence. Mention must now be made of a fourth hormone which is closely allied to the gonadotropic principle of the pituitary. Zondek and Ascheim discovered that the urine of pregnant women contains a gonad-stimulating hormone which behaves in very much the same way as the anterior pituitary sex hormones. The urinary principle, which is called prolan. produces the same effects on the genital apparatus of infantile

animals as do pituitary implants, and appears to possess the same physical and chemical properties. It is generally believed, however, that prolan is not identical with the gonadotropic hormone of the pituitary, and it is thought to be produced in the placenta. Prolan is so easy to obtain that it is employed for its gonadotropic effects far more frequently than anterior pituitary extract, and there are a number of commercial preparations on the market. The interesting discovery has recently been made that extracts of the anterior lobe of the pituitary possess the property of synergizing the action of the urinary hormone, and this finding promises to be of the greatest assistance to those engaged in clinical practice. If infantile mice are injected with prolan and anterior pituitary extract simultaneously, in amounts which by themselves cause little or no ovarian development, a most striking stimulative effect is obtained, the ovary being studded all over with corpora lutea. The subject has been studied by Evans, Simpson and Austin (12), who consider that the synergistic influence of the anterior pituitary is due neither to the growth-promoting nor to the gonad-stimulating principle, but to quite an independent factor.

It will be convenient to consider here some of my own experiments which have a bearing on a number of the points referred to in this paper. My object in undertaking them was to ascertain the degree of potency possessed by the various commercial preparations, and at the same time to make certain observations which I thought might subsequently prove useful in the treatment of mental patients. Six immature and three mature male rabbits were given daily injections of prolan for a period of 14 days, a similar number of animals of the same age (mostly litter mates) being used as controls. Male rabbits were chosen in preference to female partly because the male sex organs are admittedly more difficult to stimulate with gonadotropic substances than the female, and partly because it was intended at a subsequent date to treat male patients with the same material. The preparations of prolan used were ordinary commercial extracts of pregnancy urine, and the dose employed varied from 100 to 300 rat units per day. The rabbits were weighed weekly, and kept under standard conditions as regards food and housing. After death the thyroids, suprarenals and testicles were weighed and sectioned, and the bone-marrow was also examined. No change in the behaviour of the rabbits which were undergoing medication was noted, and the alterations in weight were very similar in the control and experimental groups. Post-mortem examination showed a certain amount of variation in the weights of the thyroids, suprarenals and testicles, but no consistent data were obtained. Microscopical examination of the suprarenals revealed negative results, but there were slight histological changes in the testicles and thyroids of some of the treated animals. In four of the latter the testicular tubules contained much fewer spermatogenic cells than those of the controls, and the existing cells appeared to be in a state of degeneration. In no instance was there an increase of interstitial tissue,

nor was there any evidence of premature spermatogenesis among the immature rabbits. On the other hand, the thyroids of some of the animals which had received prolan appeared to have undergone slight stimulation, as evidenced by diminution of colloid and epithelial thickening. This change, however, was not marked.

It will be gathered from the foregoing brief description that the effect of commercial prolan on male rabbits was disappointing, although the preparations used were unquestionably active when administered in quite small doses to female mice. Not only was there no stimulation of either the intra-tubular or interstitial cells of the testis, but in four instances there was actual degeneration of the germinal epithelium. Similar degenerative changes within the tubules have been noted by Engle (13) in rats, after treatment with extracts of pregnancy urine and anterior pituitary, but in Engle's animals there was an increase in the interstitial cell mass. The slight stimulative effect exerted by the prolan on the thyroid gland is interesting in view of the fact that Starr and Patton (14), as a result of a series of metabolic and histological studies, came to the conclusion that there was no thyrotropic hormone in pregnancy urine.

Owing to this complete failure to obtain gonadotropic effects in male rabbits with prolan, it was next decided to combine the latter hormone with anterior pituitary extract, since a definite synergism operates between the two. For this purpose four adult male rabbits were employed, and, as before, they were controlled by litter mates. From 50 to 150 guinea-pig units of an anterior pituitary extract known as ambinon, combined with a similar number of rat units of prolan, were injected daily for a period of a week. The treated animals lost no weight, and exhibited no manifestation of importance during life. The post-mortem findings were, however, of considerable interest. The seminal vesicles of the animals which had received the injections were much larger than those of the controls, and were distended with jelly-like material, while the testicles showed a definite increase in weight. Microscopical examination of the testicles revealed a pronounced hyperplasia of the interstitial cells, the latter being not only more numerous, but also larger than those of the controls. The extent of this interstitial hyperplasia varied in direct proportion to the dose of hormone given. The seminiferous tubules were well stocked with cells, and there was not a trace of degeneration. Figs. 1 and 2 illustrate the average microscopical appearance of the testicles of the experimental and control animals. In Fig. 2 it will be noticed that the interstitial cells occur in scanty islets, while in Fig. 1 they occupy much larger areas between the tubules. Since these cells are responsible for the hormone which stimulates the growth of the accessory sex organs, it will be readily understood why the seminal vesicles of the experimental rabbits were so large. The thyroid glands of both the experimental and control group were in a very active state, and there was little histological difference between the two. In all probability this was due to the fact that all the rabbits had been fed on cabbage, which, as Spence and

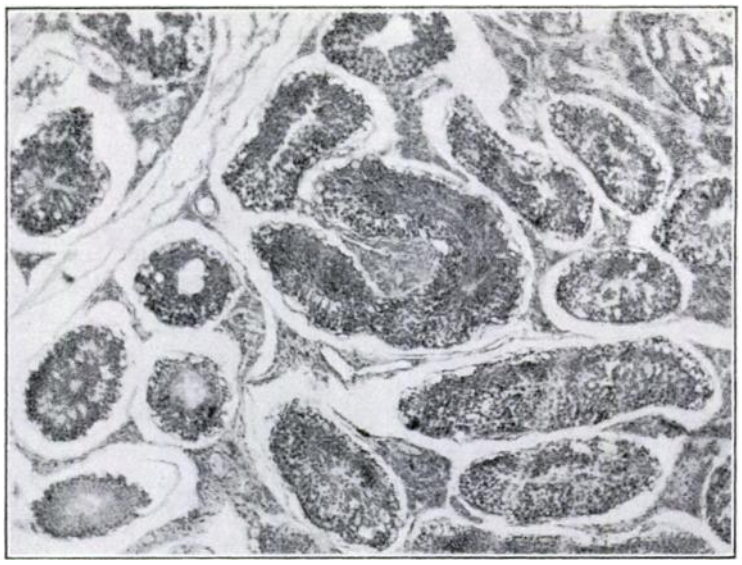

FIG. 1.—*Rabbit No.* 114 illustrates combined effect of prolan obtained from pregnancy urine and anterior pituitary extract on testicle of adult rabbit. Note increase of interstitial cells. (× 92.)

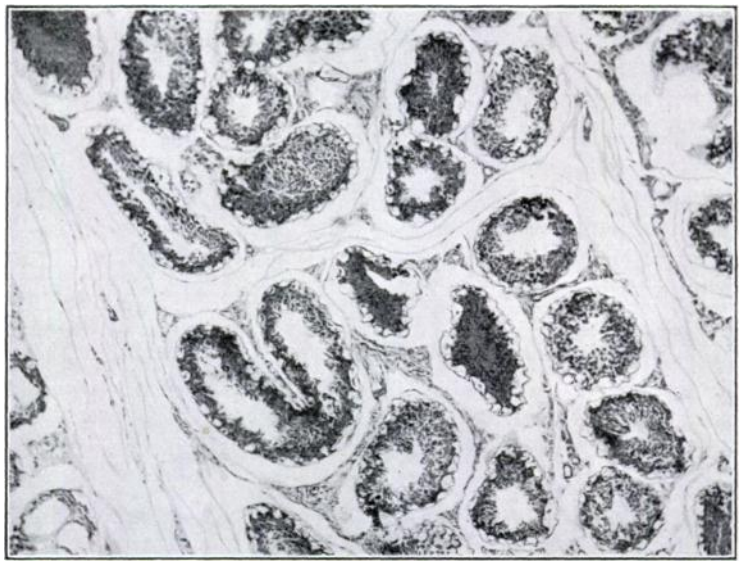

FIG. 2.—*Rabbit No.* 115. Testicle of control rabbit of similar age and breeding to No. 114. (× 92.)

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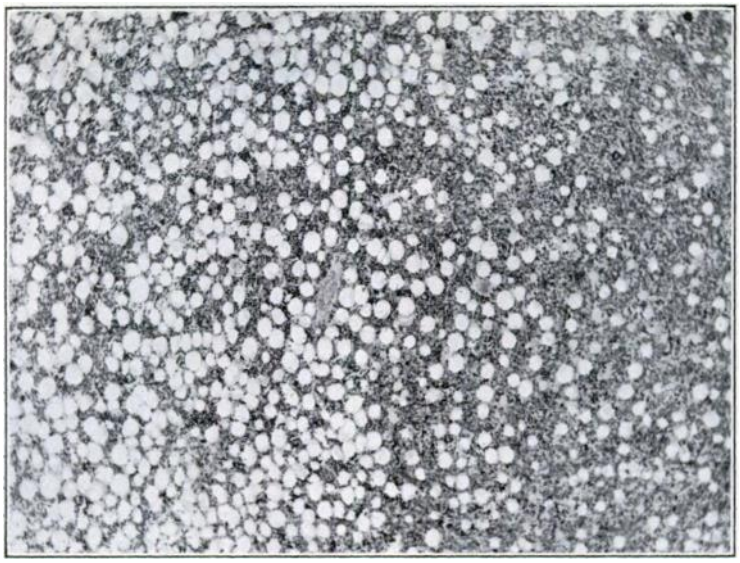

FIG. 3.—*Rabbit No.* 114 illustrates combined effect of prolan and anterior pituitary extract on bone-marrow of rabbit with testicle as shown in Fig. 1. Note diminution in size of fat spaces, and marked increase in blood-forming elements. (× 62.)

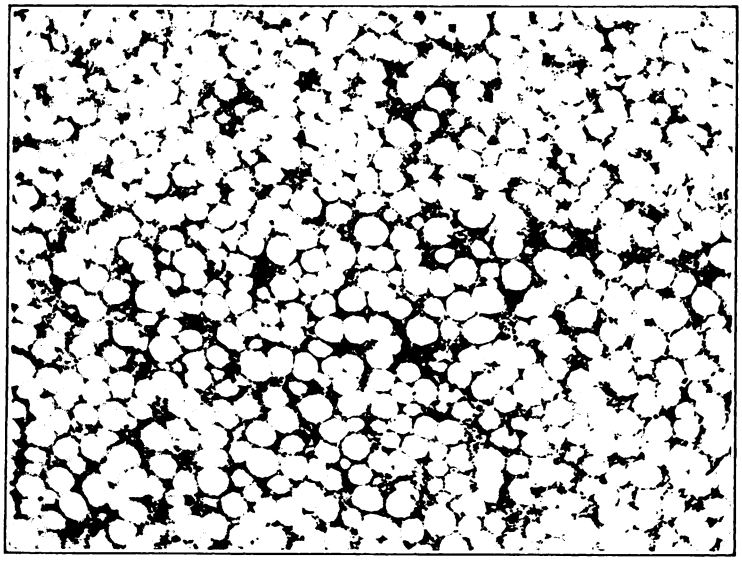

FIG. 4.—*Rabbit No.* 115. Bone-marrow of normal control animal. (× 62.)

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others have demonstrated, exerts a stimulative influence on the gland. There was, however, a piece of evidence of a different kind which indicated that the thyroids of the injected animals were elaborating a much greater quantity of hormone than those of the controls. In a previous publication (15), I have amply demonstrated that, if thyroxine is injected into rabbits, a very pronounced hyperplasia of the bone-marrow is produced, which is due apparently to a rise in the basal metabolic rate, with a consequent increased demand for oxygen on the part of the tissues. The bone-marrow of the four rabbits, which had been treated with prolan and anterior pituitary extract in combination, exhibited a similar marrow hyperplasia, and this varied in degree with the doses employed. Figs. 3 and 4 illustrate this marrow hyperplasia very clearly. The organ of the treated animal shows a great reduction in the size of the fat spaces, while the intervening tissue, which, of course, consists of developing blood-cells, is enormously increased. The finer details of the marrow structure were very similar to those found after thyroxine medication, and seemed to prove conclusively that the thyroid gland had undergone stimulation as a result of the injections. It would have been preferable if in the above-mentioned experiments a larger number of rabbits had been employed, but the high cost of the ambinon rendered this impossible. However, similar results were obtained in another series of animals in which prolan was combined with a crude anterior pituitary extract prepared by me from material obtained at a neighbouring abattoir.

The experiments with ambinon and prolan show that there are now preparations on the market which are able to exert a definite stimulative influence on the thyroid and testicle, causing these organs to elaborate an increased amount of their respective hormones. It is interesting to note that while prolan alone appeared to produce degeneration of the spermatogenic cells, when given in combination with anterior pituitary extract no such injurious effect was produced, while the interstitial cells were definitely stimulated. Although the ambinon itself contained a certain amount of gonad-stimulating principle, it is probable that the greater part of the testicular reaction was due to the synergic factor to which reference has already been made.

Clinical Applications.

The foregoing developments in endocrinology provide the psychiatrist with much food for thought. We find that the pituitary gland, which is so closely connected with the diencephalon, exerts a profound influence, not only on the rate of bodily growth, but also upon sexual development and metabolism. Most, if not all, of these functions it exercises through the medium of other members of the endocrine group, and the latter in their turn have the power of influencing the pituitary. These inter-relationships are very complicated, and we are still far from understanding them, but it is clear that no single endocrine gland can undergo stimulation without the production of general

hormonal disturbance. It would seem that one of the functions of the pituitary is to supplement certain forms of nervous activity by the initiation of a series of chemical changes in the body, and that in this respect it is subservient to the organic needs of instinct. This is suggested by the intimate relationship that exists between the pituitary hormones and the process of reproduction, which itself represents the end-result of a series of psychological events which have been prompted by the sexual instinct. The latter, however, energizes much more of our mental life than that concerned with the selection and wooing of a mate, and it is difficult to believe that under these circumstances the pituitary gland is not implicated. One of the tasks before the psychiatrist of to-day is the correlation of the various mental processes traceable to the sexual instinct with changes occurring at the endocrine level. That the sex hormones do influence mental processes to a very marked extent is suggested by the personality transformation which normally takes place at the time of puberty and adolescence, as well as by the minor mental disturbances of the menopause. It is, however, from a study of the grosser forms of mental disorder that we may expect to derive most knowledge of psycho-sexual functioning, and this brings us once again to the subject of dementia præcox, which has long been suspected of being primarily an endocrinopathy.

Much work on the pathology of dementia præcox has been performed by Mott (16), McCartney (17), Dercum (18), Matsumoto (19), Fränkel (20) and Geller (21), but it is only possible to mention the investigations of Mott and McCartney. Mott found that in dementia præcox there was a regressive atrophy of the reproductive organs, which he attributed to an inborn lack of specific vital energy in the germ-cells, causing the majority of the latter to fail to maturate and to die prematurely. He did not regard the atrophy of the gonads as being the primary cause of the disorder, but rather as the reflection of a general failure of biological activity which, while it affected all the structures of the body, was most pronounced in the brain and reproductive organs. He further associated this lack of vital energy with a low level of oxidation —a point which has been confirmed by subsequent observers. More recently McCartney has investigated the subject from a somewhat different standpoint. He examined 20 Chinese eunuchs abandoned after the dissolution of the Imperial Court in Peking, and 3 Skoptsi who had been driven from Russia and taken refuge in China. He claimed that they showed typical dementia præcox or schizoid character—good intelligence and orientation, but distinct changes in affect. He also examined 110 living male and female schizophrenes, and found that 60% of the men were eunuchoid in type, while 52·5% of the women had undoubted ovarian disease. He concluded that in dementia præcox the gonads are consistently degenerated or hypofunctioning.

It follows from these researches that dementia præcox is a malady which affords abundant material for study from the standpoint of modern endocrinology. If we have at our disposal therapeutic preparations which have the

power of stimulating the gonads and raising the oxygen consumption of the body, they should be of assistance to us in treating a disease where such deficiencies occur. Accordingly it was decided to investigate with an entirely open mind the effects of prolan on seven selected cases of dementia præcox. Although this preparation had failed to stimulate the gonads of rabbits, it was considered worthy of clinical trial in view of the good results claimed for it in the treatment of undescended testicle in man. Male patients were chosen for the investigation rather than female for two reasons. In the first place the symptoms of the male insane are not so liable to transitory change as those of the female, and secondly, the male nurses of the average mental hospital are far more experienced than the female, and, consequently, their reports are more valuable in the research worker. It was not anticipated for one moment that anything to the nature of a cure would be obtained by the doses of prolan which it was proposed to employ; my object was to observe the patients very closely under standard conditions, and to note any temporary change in their physical or mental state which might result from the treatment. Since dementia præcox is a disease that is liable to fluctuations in intensity, and in which transitory amelioration may follow such minor occurrences as a change of ward, or the focusing of the patient's interest on some hospital occupation, the cases under investigation were confined to a single ward, not encouraged to work, and observed individually for some time before the endocrine therapy was commenced. The prolan, which was the same as that given to the rabbits, was administered either subcutaneously or intramuscularly, and, for the convenience of the reader, the doses employed and the duration of the treatment are given in the following table:

Case No.	Duration of treatment.	Total dosage (R.U.).	Maximum dosage in one week (R.U.).	Thyroid enlargement.
1	9 months	28,300	2,800	+
2	1 month	2,300	700	0
3	1 ,,	2,600	700	0
4	5 weeks	3,100	700	0
5	1 month	2,400	700	+
6	6 weeks	9,200	1,500	0
7	16 days	1,600	700	+

The temperature, pulse, blood-pressure and measurement of the thyroid were ascertained daily during the period of medication, except in Case 1, where these observations were recorded on 240 occasions in 9 months. All patients were weighed weekly prior to, during, and subsequent to the treatment.

In most instances in which the hormone was administered intramuscularly a rise of temperature occurred on the evening of the day of the injection, but this pyrexia had usually subsided within 24 hours. The pulse-rate was little

affected, and, except when large doses were given, the patients did not seem to suffer any inconvenience, continuing to take food in the ordinary way. The behaviour of the blood-pressure was, however, interesting, and merits consideration. In many cases of dementia præcox the systolic blood-pressure is abnormally low, and remains like this for years on end. Case 1 was a typical example of this. He had been under observation for a long time and his blood-pressure had always been low. The systolic pressure varied between 105 and 118, being usually about 110, which certainly may be regarded as low, in view of the fact that he was 31 years of age. During the first five weeks of his treatment the blood-pressure was taken by the auscultatory method on 24 occasions, and was found never to exceed the previous upper limit of 118. After he had received 2,000 R.U. of prolan it rose to 140, and during the last five months of the treatment, although readings were taken on 85 occasions, the systolic pressure was never below 125, and usually above 130. Although fully aware that blood-pressure findings should be interpreted with caution, I cannot help feeling that the rise of pressure noted in this case was definitely attributable to the prolan. That it was genuine and sustained is beyond all question, and since there was no other circumstance to account for it, it is logical to regard it as being due to the injections. Of the other six cases, five exhibited normal blood-pressure readings from the start, and these were quite uninfluenced by the treatment. In Case 4, on the other hand, the average systolic pressure was abnormally high prior to the injections, and in this instance a reduction of some weeks' duration was effected by 850 R.U. of prolan. While it is difficult to reconcile these conflicting findings, one is left with the impression that they possess some significance in regard to endocrine functioning. It seems fairly certain, however, that prolan, when given in moderate doses, does not produce an injurious effect on blood-pressure, because in one case of severe hyperpiesis (outside this series) in which the preparation was tried, the blood-pressure (230/145) remained entirely unaffected.

Although the prolan obtained from pregnancy urine is not usually regarded as possessing any thyroid stimulating properties, in view of the fact that the glands of some of the treated rabbits had shown changes in this direction, a careful examination of the patients' thyroids was made. The circumference of the neck at the level of the thyroid gland was ascertained daily for a preliminary control period as well as during the injections, and by using great care a fairly reliable series of figures was obtained. Three out of the seven patients showed definite enlargement of the thyroid as a result of the medication. This made its appearance after about a fortnight's treatment, when approximately 1,200 R.U. had been given. It was unaccompanied by any signs of excessive thyroid secretion, such as rapidity of pulse, nervousness or loss of weight, and it would scarcely have been noted if careful measurements of the neck had not been made. The most remarkable feature about it was that it persisted for months after the prolan had been discontinued, and in one instance

was quite unaffected by the simultaneous administration of iodine in the form of potassium iodide.

We now come to a consideration of the effect of the injections on the mental condition of the patients. The type of case chosen was one in which any mental improvement could be studied *objectively*, without any reference to the patients' subjective experiences, and in order to obviate all possibility of suggestion, no questions relating to health were asked during the investigation. The cases had all showed marked dynamic failure, viz., loss of ambition and interest in the ordinary affairs of life, withdrawal from reality, loss of affection for those previously loved, slovenliness and neglect of personal appearance, unsociability and general indolence. All these symptoms appear to denote a failure of psycho-physical energy, which might conceivably involve endocrine disturbance or defect, and prove susceptible to substitution therapy.

Two out of the seven patients made a fairly good recovery, and were ultimately discharged from the mental hospital, but after carefully reviewing all the relevant facts, I cannot bring myself to believe that their cure had anything to do with the prolan. One of them (Case 7) began to show improvement 26 days after the last injection. Up to that time he had been entirely mute, but he now began to ask questions, and to exhibit normal animation and interest. He realized that he had been ill, and he gave a most interesting and vivid description of the bizarre phantasies in which he had been indulging. All this would have been most gratifying from the standpoint of the investigation if he had relapsed when the injections were discontinued, but he made an uninterrupted recovery, and as far as I know has remained well ever since. The second case (Case 5) began to show improvement ten weeks after the termination of his treatment. He had hitherto been mute, solitary and disinterested, but all his previous animation returned, and he conversed freely and rationally. In due course he was discharged, and he has remained well for six months. It is most important to emphasize the fact that not infrequently cases of dementia præcox make a very fair recovery without having received any specific therapy, and, consequently, clinical improvement should only be attributed to a particular line of treatment when it directly follows this. In the two cases in question recovery was delayed for too long a period after the termination of the injections to be of any definite significance. On the other hand, it is worthy of note that in each of these cases the thyroid gland enlarged in response to the prolan. The remaining five cases, which were very advanced, showed absolutely no improvement, and, indeed, in one instance mental deterioration appeared to be accelerated. They were, perhaps, hardly fair tests of the efficacy of gonadotropic treatment, for if their testicles had reached the advanced stage of degeneration depicted in Mott's photographs (22), it would have required enormous doses of prolan to resuscitate them.

On the whole, then, these results are disappointing, but before passing final judgment on them we must ask ourselves two questions: Firstly, were

the preparations used really gonadotropic for the male, and secondly, were the doses employed adequate? It has already been shown that no gonadotropic effect was obtained in male rabbits with extracts of pregnancy urine, but against this must be quoted the encouraging results reported by Spence (23) and others in the treatment of undescended testicle in man, when using a very similar preparation. With regard to the doses given, they were admittedly inadequate, if calculated on the basis of body-weight, and one must not forget that Kaufmann (24) found it necessary to employ truly colossal doses of œstrin before he was successful in producing endometrial changes in castrated women. I should like to have tried the effect of much larger doses of prolan on my patients, but this was absolutely out of the question owing to the expense involved. My thoughts have, therefore, turned in another direction.

An account has already been given of the very marked effects produced on adult male rabbits by a combination of anterior pituitary extract and prolan. While prolan alone failed to stimulate the genital apparatus, when combined with anterior pituitary it effected enlargement of the seminal vesicles and proliferation of the interstitial cells of the testes. There was also marked hyperplasia of the hæmatopoietic tissue of the bone-marrow, which suggested a rise of basal metabolic rate and an increased consumption of oxygen. It was decided to try the effect of this combination of hormones on two cases of dementia præcox, one of which (Case 1) had previously been treated with prolan alone. The initial results left no room for doubt that we were here dealing with material which was capable of producing very profound biological effects. As a preliminary, a number of injections of anterior pituitary extract alone was given to each patient. Beyond an evening rise of temperature on the day of the injection little abnormal was noted, the body-weight being very little affected. When the same amount of this extract was combined with prolan, however, the pyrexial reaction was much more pronounced and prolonged, and there was considerable tachycardia. There was also a very marked loss of weight, in each case amounting to 7 lb. in a fortnight. Case 1, which had been under close observation for the previous nine months, had never previously lost weight, and had not exhibited tachycardia. Both patients quickly developed toleration for the injections, and no further loss of weight has occurred. The treatment is continuing, and it is too early as yet to pass judgment on it, but on the whole I am rather favourably impressed.

Conclusions.

The foregoing investigations represent little more than gropings in the dark in a subject which is much in need of elucidation. It seems probable that all instinctive and emotional activities are accompanied by subtle alterations in hormonal balance, and that these in their turn influence neuronic processes. The close connection between the diencephalon and the pituitary gland lends support to this view, for, as we have seen, the pituitary is the master gland of

the body, and on it depends the degree of functioning displayed by a number of subsidiary glands remotely situated from it. It is easy to imagine how a profound emotional disturbance might be perpetuated by endocrine disharmony, and prove susceptible to substitution therapy. Much stress has been laid in this paper on the part played by the pituitary in the development and activity of the reproductive organs, because it is felt that these physical processes have an important bearing on the force and vigour of the sexual instinct, which supplies the driving force of so much of our mental life. Attempts have been made to stimulate the interstitial cells of the testis in cases of dementia præcox, not because degeneration of these elements is regarded as the primary cause of the disease, but because it was hoped by remedying this defect to break a vicious circle. It is fully realized, however, that the dynamic side of sex involves much more than a mere stimulation of the genital apparatus. Probably every hormone in the body plays its part in co-operating with this great instinct, and what is wanted for dementia præcox is something which will produce a generalized stimulation of this nature. A combination of anterior pituitary hormones suitable for hypodermic injection would appear to be the ideal therapeutic agent, but until this preparation is on the market we must content ourselves with minor laboratory and clinical experiments such as I have been describing. Sufficient has been said to show that the psychiatrist has much to learn from modern endocrinology, provided that he sets out on his researches with an open mind and has no expectation of being able to work miracles.

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Discussion.

Dr. F. L. GOLLA said he wished first, as he was sure all in the room would wish to do, to congratulate Dr. Power on this exceedingly courageous piece of work. It had been undertaken in the face of many obstacles, and, he was sorry to say, had not received that encouragement it ought to have had from those who had means to finance research. Dr. Power had in this paper given the foundations of the type of research which would be necessary to elucidate problems connected with the affective life of the psychotic individual.

There was, however, one fundamental question on which workers had to form, if they could, some judgment before proceeding to apply the results of endocrinology

to psychiatry. Practically every function—and there were many besides those to which Dr. Power alluded—was under the direct control of the central nervous system. The trouble with the endocrinologist was that he forgot the central nervous system; and the trouble with the neurologist was that he tended to forget the existence of hormonic stimulants. There was every reason to think that practically all the functions with which Dr. Power had dealt that morning were initiated by the group of centres the physiology of which the profession was only now beginning to appreciate; the metabolism, the chemical and physical regulation of the body heat, gonadal function, the regulation of the chemical metabolism of the liver and pancreas, the regulation of the distribution of the blood supply and a thousand other functions were directly stimulated by the diencephalic centres. The problem which presented itself was, had one to do with a primary hypo-function of nervous material, or with a primary hypo-function of hormonic material? At the present moment it was impossible to pronounce on the subject. So far there was only one bit of evidence that the hormone-producing bodies were interfered with in any form of psychosis, and that was the celebrated work of Mott on the testicle, and it was necessary to receive even that piece of evidence with due caution. Those who had bred rabbits knew that if they could keep a buck rabbit for two or three years—two as a minimum—from any possibility of copulation, there was a degeneration of the testicle, and the rabbit became, after four or five years, impotent. There were some German observations which were made on reservists who were sent to the Russian Front during the war, and were housed far away from any village or town, who had so little privacy that even masturbation could not take place. The men were kept for two years under those conditions, and it was found in practically every case that they had become asexual, and in some there appeared to be a permanent atrophy of the testicle.

He, the speaker, was not connected with clinical psychiatry sufficiently to know whether it was a possibility that the obsessions and the mode of life of the schizophrenic patient were of such a nature that he could be cut off from sexual stimulation, and whether, in consequence, atrophy of the testicle might occur. That was the only objection which could be urged against Mott's results. It would be interesting to hear what could be said on that point. Apart from that, no histological examination had given any foundation for the idea that there was a disturbance of the hormonic apparatus, whether thyroid or pancreatic, or any different function of the liver or any other gland. Physiologically, what one found was a hypo-function of those glands. There was a slowing of the sugar metabolism, and it was found that secretion of gastric juice took place in these patients more slowly than in the normal person. In fact there was a general slowing down, including the vascular system; but, at present, there was no evidence that the state of affairs was primarily due to the hormonic apparatus, rather than to a weakness of the portion of the central nervous system which governed all those functions. Workers on this subject were only just beginning to get an idea of the extraordinary power of the central nervous system over the functions of the body. He himself had not believed, until it was confirmed, that it was possible to obtain conditioned reflexes of antigen production; i.e., one injected an animal to produce antigen, and each time one blew a whistle or gave some stimulation it acted; until at last water was substituted, and the same action occurred. That showed that in these functions there was at work a profound nervous influence; and what had to be decided was whether one could implicate the nervous apparatus, or the hormonic apparatus. There was, he thought, only one solution, and that was when the biochemist was ready to pronounce on the hormonic action of any gland by biopsy or by a study of the hormonic secretions in the blood, and was able to say definitely that one had here to deal with a primary hormonic disturbance. Even then workers would still be in the dark, because the whole thing worked in a circle, and the great question to solve would be whether the hormonic disturbance arose from the diencephalon primarily, or whether that was itself secondary.

He mentioned those matters because it was so important at the present moment to devise some scheme of work to ascertain on which side the attack was to be conducted.

There was another point which was mentioned earlier in the paper, namely, the question of the evaluation of the bodily concomitants of emotion; as to whether it was "the stone casting a ripple", or whether the ripple was the real thing. Anyone who had stepped off a pavement and seen a motor bus come along and had stepped hurriedly back was familiar with the sensation of going hot all over, and he might perhaps remember that he did not do so until he was actually back on the pavement again. He, the speaker, himself made the following experiment some time ago; it might afford a clue to an understanding of the part which the emotional apparatus played in the general manifestation of the emotions. Every emotional reaction had a very long period of latency, whether one took increased breathing, or the sweat reaction, or the increase of blood-pressure, or the tightening of muscles. In each case it was found that the reaction did not take place until two seconds after the occurrence of the emotional stimulus: The experiment was as follows. He subjected a man to two forms of emotional stimuli: (1) flashing a terrifying magnesium light; (2) firing a pistol behind the man's ear. The man was required, on receiving one stimulus, to press key "A", and on receiving the other stimulus to press key "B". He recorded the reaction galvanometrically. Photography was used for the recording, and it could be seen which of the two keys was pressed by the man. One ten-thousandth of a second after the stimulus occurred the galvanometer record gave a little jump. It was not from the brain; it was the same in an animal which had no brain. It was a mid-brain reflex. And then the curve of the galvanometer went on, and one-tenth of a second after the light had been fired off, the man experimented on selected the right key and pressed the signal; in other words, he had recognized the type of emotional stimulus and had acted on it. But the galvanometer showed nothing until two whole seconds had elapsed; the man had recognized the kind of stimulus. It was only later on that the general bodily reinforcement occurred—an event which was called emotion. In other words, one could not impugn the intellectual process, and one could not say it was affected primarily by the occurrence of the emotion, as the latter was a late phenomenon. It was the adaptation of the body to the type of reaction. He mentioned that because he thought it was necessary to realize that if we were without emotion we were able to form a certain amount of corrected judgment, but were unable to pursue the course of conduct afterwards which might be elicited by the emotion. One could distinguish between the intellectual response and the later emotional response.

There was, he considered, one other matter which came into this emotional question, namely, how far, even if emotions were subdued—either by loss or by the hormonic influence, or by degeneration, or by hypo-function of the nerve-cells, or the diencephalon—how far the psychotic was capable of behaving like a normal person in a difficult situation. One of the great opportunities lost during and after the War, immediately after it, was that of seeing how far it was possible to represent cortical movements in amputation cases, i.e., how far one got the kinæsthetic representation of movement, and if having once had emotion and then being deprived of its mechanism, it was possible to represent in the cortex what that emotion was, and to feel it as a cortical representation. The opportunity for this mass observation had now passed. It would have been interesting to ask a man who had a limb amputated whether he had a movement in it as an act of will; also whether the psychotic whose emotional functions were in suspense could reproduce that emotional state as a psychic mechanism.

The object of his remarks was merely to emphasize that Dr. Power had given the Association groundwork for the kind of investigation which must be carried out in studies on endocrinology. But what workers now had to concentrate on was to find out whether it was primarily nervous or hormonic. That problem was just about as difficult as any that still remained to be tackled. It was required

to find out whether the substances secreted were of the appropriate kind and responded to the stimulus, or whether, in degenerated people, they ceased to have that effect.

Prof. LAIGNEL-LAVASTINE (Paris) said: I have been very pleased to listen to Dr. Power's report and I am glad to congratulate him, especially for the precision of his physiological experiments.

When listening to a report on the relations between endocrinology and mental disorders I feel myself about thirty years younger; it was indeed in 1908, at the Congrès des Aliénistes et Neurologistes de France et des Pays de Langue Française at Dijon, that I presented a report on this question of the relations between internal secretions and mental disorders.

I came back to the same subject in a report which was to be presented to the International Congress of Psychiatry inBerne in 1914, on "Internal Secretions and the Nervous System", and which was published afterwards in French by Alcan, in English in a monograph of the *Journal of Nervous and Mental Disease* (of New York), and in Italian in the *Rivista di Freniatria*.

Since then I have continued to study the relations of internal secretions and mental disturbances, especially through the sympathetic system, as it may be seen in my "*Pathologie du Sympathique*", my "*Méthode Concentrique*" and my "*Conférences de Sympathologie Clinique*".

When we consider the enormous question of the relations between internal secretions and psychic disorders we must, first, be sure that there is more than mere coincidence. I have thus observed, when I was Prof. Gilbert Ballet's collaborator in the Clinique de Maladies Mentales at St. Anne, before the war, a typical case of myxœdema which was at the same time a general paralytic. At the autopsy we discovered the thyroid completely atrophied, weighing only 2 grammes. The brain showed the well-known lesions of general paralysis. There was in this case a double localization of hereditary syphilis.

More recently I have seen a similar case to those related with his usual humour by our President. It was that of a tall young man who, to increase his sex-appeal, had stolen a motor-car and had gallantly offered a seat to a young beauty. This thief was not only a big acromegaloid man through hypertrophy of the hypophysis, but at the same time he was the son of a tabetic and thus a congenital syphilitic, and I am inclined to think that the theft was more closely associated with the latter affection than with any disorder of the hypophysis.

We will now consider some anatomo-clinical relations explained by certain facts which I have been observing during thirty years.

First, in some cases of manic-depressive psychosis the lesions of the thyroid gland are so evident that in an article of the "*Actualités Medicales*" of Prof. Pierre Marie I thought it was possible to distinguish periodical mental disorders of thyroid origin. The disorders of the thyroid gland which produce these troubles seem to occur in two phases: (*a*) hypertrophy, (*b*) atrophy. The thyroid gland is sometimes reduced to a minimum and transformed by sclerosis.

In the relations between endocrinology and psychic disorders, we must not think that the endocrine disturbances always appear before the mental disorders. It is possible to observe the contrary.

For instance, I made autopsies on a great number of agitated patients who died from cardiac collapse, and I observed in the suprarenal glands the complete disappearance of the phosphorated lecithins, which are coloured by osmic acid, and normally situated in the reticulated and the internal portion of the fasciculated zones. It seems to me that the agitation of the patient has exhausted the lecithin reserve of the suprarenal glands.

There is another histological relation which seems to be very interesting. In a systematic study of the parathyroid glands of 64 mental cases, I found with Duhem a complete eosinophilic transformation in nearly all the parathyroids of the senile dements.

This coincidence seems to be quite explicable now that we know the role of

the parathyroids in the metabolism of calcium, and the role of calcium in the metabolism of the brain.

Another relation between endocrinology and mental troubles is to be found from the chemical point of view. A good number of anxious patients seem to have an alkaline urinary reaction. This alkalosis is generally accompanied by vagotonia and hypocalcæmia. I noticed, with Drs. Souffland and Pouchet, that treatment by ultra-violet rays fixes calcium, acidifies the humours, reduces vagotony and at the same time calms anxiety.

I will not say anything else on the relations between this hypophysis and other glands and mental disorders, but I can say that I have obtained, in a great number of cases, very good results by the combined anti-syphilitic and pituitary gland treatment.

I will now say a few words on a special endocrino-sympathico-psychical syndrome which I have called " Endocrino-névrose hypotensive ". It generally concerns tall and thin women with " acrosphyxia ", exaggeration of the secretion of the ovaries, emotional, and who easily become anxious. These patients are often helped by combined hypophysis and suprarenal treatment.

In these complex cases, Hirsch's interferometric method has given me a good number of interesting results. When carefully interpreted, this method can be used in general practice. Another method is a very old one: it is the study of the dreams of the insane patients. In a certain number of women treated by " androstine " an exact and regular analysis of the dreams showed the regular appearance of images of the sexual type, as in Freud's symbolism. So we see the direct and indirect relations between endocrine activity and psychic activity.

It is because of the great usefulness of these investigations, in general practice, that I have ventured to refer to them here after listening to Dr. Power's report.

Major J. E. DHUNJIBHOY, I.M.S., said he felt very much indebted to Dr. Power for this very interesting contribution. He would like to ask him whether, in his experiments, he found that the sexual characteristics were increased in the rabbits he studied. He also asked whether the animals' activity was increased. Dr. Power had remarked that the carrying out of these experiments was very expensive. He, the speaker, had been carrying out experiments in a large institution in India. In those researches he was not using injections of prolan, but was performing vasectomy and ligature. He first used rats and rabbits in the investigation, and then proceeded to use goats, monkeys and dogs. Later still he applied the knowledge he obtained to human patients, and with the latter he obtained equally good results. Members would know that Eugene Steinach, in Vienna, carried out work by means of this operation, and that he obtained wonderful results. That investigator—being a pioneer—was, of course, laughed at at first; but later the results were confirmed by Dr. Schmidt. Some thousands of experiments were done in all by Dr. Clarke, of Michigan University. The speaker had studied the accounts of those experiments in many countries, and had found proof of the results in his own work. He advised anybody working at this subject to try the effects of vasectomy. Of the 100 cases he had experimented with he had been able to discharge at least 50 cases of dementia præcox after that operation. The method of procedure was not costly; it was merely a question of an operation lasting 10 minutes, under local anæsthesia, and it was well worth trying in cases of dementia præcox.

Dr. DAVID SLIGHT (Montreal) said that for some years this subject had been to him one of great interest. He was sorry to hear that Dr. Power found so much difficulty in obtaining the extracts he required, and that his work proved so expensive, as from America he could be supplied with gallons of it.

Dr. Golla, in the course of his remarks, had stressed one difficulty in respect of the psychoses, i.e., many of the different effects observed were due to nervous changes, and it was difficult to know how much was due to this and how much to changes in the endocrines. But now that anti-hormones were known, the subject became more complicated than ever. There were gonadotropic substances and

thyrotropic substances, and now there were anti-gonadotropic and anti-thyrotropic ones. It did not seem that the subject would be carried very far in regard to specific endocrine therapy until specific tests had been established for the presence of these hormones in the blood, and also tests to show the presence of the so-called anti-hormones. In dementia præcox the speaker and his co-workers failed to get results with the Vienna A.P.L., like the preparations which Prof. Moore got from the placenta.

This problem of the central nervous system versus endocrines was well exemplified in one or two cases the speaker had seen recently. They were cases of dementia præcox, with a basal rate of −20—he would like to know whether Dr. Power in his work took the basal metabolic rate—and he treated one of these cases by psycho-therapy, and it cleared up completely. Unknown to the speaker, the patient had, in a previous episode, been treated with various endocrine extracts, including thyroid and prolan, and after a time he had cleared up. His most recent case he had shortly before he left Montreal. It was that of a young man, with a basal rate of −20. He was subject to narcolepsy, and had been treated with large doses of thyroid without effect. Then it was found that he had anti-thyrotropic substance in the blood. The speaker used psycho-therapy, and apparently there was a good result, as he had been free from his narcolepsy for months.

It was of great interest to him to know that this work on endocrinology was going on in Britain, and he thought that if the question of expense was allowed to interfere with its continuance it would be very unfortunate. He therefore would like to know whether Dr. Power took basal rate readings, to ascertain whether there was a hyperfunctioning or a hypofunctioning of the thyroid.

To illustrate the difficulty, he wished to refer to the case of a woman who showed signs like those of dementia præcox, and was at first diagnosed as schizophrenia; but as she began to have left-sided attacks with exophthalmos on one side, with flushing also, and an increase of temperature on one side, the diagnosis was changed to that of brain tumour. Her basal rate reading was −40. She did not respond to thyroid up to 20 gr. a day, neither did she respond to thyroxin. After some years there was an autopsy, and a degenerative tumour was found infiltrating the diencephalon and the lower basal ganglia.

It would thus be seen that, as Dr. Golla said, the difficulties were very great; and, at the present time, workers had either to wait for endocrinologists to work out the specific tests for these substances in the blood, and further tests for the anti-substances, or one could only act on purely empirical grounds and keep on trying.

Dr. POWER, in replying to the discussion, said one question he was asked was as to the effect on the weight of the rabbits used of injections of prolan and pituitary extract. In answer to that, he had never discovered any effect; the rabbits experimented on seemed to gain weight under the conditions in which he kept them. In the rabbits which he treated with a combination of anterior pituitary extract and prolan he was never, in the immature rabbits, able to make the testicle descend, and he never obtained in those animals a premature spermatogenesis. He found that changes occurred in adult rabbits; there was, in them, an increase of interstitial tissue, and enlargement of the vas deferens and seminal vesicles. The testes of those animals were always heavier than the testes of the controls. But there was a good deal of variation in the testicles, and in the penis, of control animals also.

With regard to the metabolic rate, he was doing his work in a tiny laboratory, and it possessed no means of taking the basal metabolic rate of animals. He had tried to take these readings in the case of patients, but it was not very satisfactory.