December 21st, 1907. Died. *Post-mortem* examination showed intestinal obstruction. Intestines much matted together and distended. This was evidently the cause of death.

III. Black and White Doe (not full grown).

November 23rd, 1907. Index 2.0. Weight 1,510 grams.
November 24th, 1907. Complete thyroidectomy.
November 25th, 1907. Index 1.4.
November 26th, 1907. Index 0.7.
November 27th, 1907. Index 0.4.
November 28th, 1907. Index 0.2. Weight 1,400 grams.
November 29th, 1907. Index 0.56. Rabbit seems ill.
½ c.cm. thyrocol given hypodermically.
November 30th, 1907. Index 0.74. ¼ c.cm. thyrocol given hypodermically.
December 2nd, 1907. Index 1.2. Weight 1,410 grams. Rabbit better.
December 4th, 1907. Index 0.9.
December 7th, 1907. Index 0.9. Weight 1,320 grams.
December 11th, 1907. Index 1.8. Weight 1,310 grams.
November 18th, 1907. Index 0.87. Weight 1,340 grams.

It is, however, well known that rabbits and herbivorous animals generally do not exhibit the effects of complete thyroidectomy and parathyroidectomy (if the latter is effected, which is somewhat doubtful) to the same extent as carnivorous animals. This probably explains the results of our experiments on rabbits.

There can be little doubt, we think, that the thyroid secretion plays some part in the calcium metabolism along, perhaps, with other functions, and the evidence all seems to point to an excretory effect.

Scordo and Franchini (Grocco's Clinic)¹¹ have recently arrived at the same conclusion from a careful examination of the calcium excretion in the urine of patients suffering from exophthalmic goitre. On the other hand, MacCallum and Voegtlin,¹² in their work on the parathyroids and calcium metabolism, arrive at a different conclusion. There must be, however, some connexion between the secretion of the thyroid gland and the calcium metabolism, even if only an intermediary one, and we shall allude to this in a later paper in regard to thyroid activity during menstruation and pregnancy.

Next, the pituitary gland has engaged our attention. It is hardly necessary to say that the gland has frequently been found to be diseased in connexion with bony overgrowths, such as one finds in acromegaly; consequently it is natural to imagine that the secretion of the gland is normally concerned in the limitation of bony deposition, or calcium retention. But, further, it is found that the extract made from the infundibular portion of the gland (Fig. 2, i)—strangely enough the non-glandular portion—has an enormously powerful influence upon involuntary muscle fibre. This effect is most marked upon the uterus, as we hope to show in a later paper. The glandular portion of the gland (Fig. 2, H) is inactive in this respect. Mr. H. H. Dale, of the Wellcome Laboratories, who has kindly furnished us with the extract, has done much good work on this subject. Professor Schäfer, however, was the first to remove the pituitary gland from the lumber room of "embryonic relics."

We have reason to believe that further investigation will show that an intimate connexion exists between the pituitary extract and the calcium metabolism. Our experiments have been limited in number, but seem to show that under the influence of pituitary extract there is an

increase of calcium in the blood, whether it is a normal or permanent effect we are not at the present moment prepared to say.

Again, adrenal extract, as every one knows, has not only a marked influence on involuntary muscle, but also causes calcium retention in the tissues. Acting upon this knowledge, Bossi¹³ of Genoa has found that osteomalacia can be much improved by the administration of this product, and experimentally it has been shown that calcareous retention in the blood vessels is brought about by its influence.¹⁴ This, however, may be a natural process consequent upon an arteritis.

Lastly, the ovaries (and testes possibly also) influence calcium metabolism, as is shown in many ways: osteomalacia has been cured by oöphorectomy, and we know that calcium retention occurs after the menopause. It is possible, also, that the part played by the internal secretion of the ovary in menstruation and pregnancy has reference to the calcium metabolism concerned in these processes.

This syndrome of facts leads one to many speculations—speculations which must be checked by careful experimentation. It seems, however, more than probable that the ductless glands preserve a balance in the calcium metabolism—as they do in many other metabolic processes—one acting anabolically, another katabolically.

It is sufficient for our present purpose to know that there is some important relationship, but we hope in the subsequent papers to indicate and illustrate more fully the connexion that exists between these glands and the functions of the female genital apparatus.

Fig. 2.—Pituitary gland (×250). Note sharp line of demarcation between hypophysis and infundibulum

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ON SLEEP AND WANT OF SLEEP.

BY

THE RIGHT HON. ROBERT FARQUHARSON, M.D.

"A BLESSING on him that invented sleep. It wraps us up like a garment," and "Sleep that does weigh our eyelids down, and steep our senses in forgetfulness." These hackneyed quotations sum up the case in favour of Nature's sweet restorer, and we all sympathize with the poor monarch who in vain sought the nightly refuge from the trials and worries of the world so freely granted to the meanest of his subjects.

I am not going to attempt to be instructive in this paper. My ambitions do not point so high, and I should like to imitate the man who, if not witty himself, was the cause of wit in others, by inducing more especially general practitioners of large practical experience to help in clearing up some still obscure points in connexion with sleeping;

and perhaps consultants and scientific experimentalists will have a look in too, and join a symposium to instruct more ignorant people what sleep really means, how it is lost, and how it can be regained quickly, efficiently, and safely. In the first place, is it not the case that there must be varieties of sleep? Unless the classical researches of Durham have been superseded by some industriously obtrusive German, it must be still taken as proved that the physiological process known as sleep results from an anaemic condition of the brain. But then there is a pathological variety. The stertorous coma of apoplexy, the anaesthetic unconsciousness of chloroform or opium poisoning, the nodding off after a heavy dinner or a good dose of the stronger wines, the sleep of utter exhaustion when we read of soldiers falling asleep on the march, little children tired out with the irrepressible vivacity of their waking hours, and the classical instance narrated by Sir Thomas Watson, and painted by Sir Charles Bell, of the man who had been operated on for tracheotomy.

"Though half a dozen candles are held close to his face to throw light on the wound, and though the surgeons, their hands smeared with blood, are still busy about his throat, making arrangements to ensure the patency of the orifice, the patient falls asleep."

I have known three very distinguished men who never could keep awake after dinner—Sir J. FitzJames Stephen, the late Sir George Campbell, and Lord Strathnairn. This illustrious general was excessively hospitable, and when I was quartered in Dublin, hardly a day passed without his orderly riding into barracks to invite some of us to dinner. Before the wine was placed on the table the old gentleman invariably began to nod, and when his forty winks were over he pulled himself together, sprinkled his face freely with cold water, and was bright and brisk for the rest of the evening. And some judges scandalize the court by their invariable habit of dropping into a deep sleep in the middle of a case about which they eventually have to give judgment. This would seem a convenient time to ask the question to which I have never yet succeeded in getting an answer—why these short naps of five or ten minutes, snatched in the middle of work, or even of play, are so extraordinarily refreshing? Over and over again, when completely tired out with the rush and bustle of London, or the strenuous increasing strain of parliamentary life, I have closed my eyes when I felt an "exposition of sleep" coming over me, and have waked up more pulled together than even by seven or eight hours between the sheets; and why, on the other hand, the same dose, administered in the early morning after the first waking, makes one sleepy, sluggish, and irritable, and easily worried during the rest of the day? How, again, are we to explain the irresistible onset of sleep which comes upon us when listening to a dreary sermon or lecture, or reading a dull book, or trying in vain to follow a wearisome debate in the House of Commons? So much, then, for the causes of sleep, and shall I be considered very stupid if I venture to ask what the precise physiological conditions are under these varied circumstances? Anaemia cannot explain them all, so will some one tell me in easy and simple language, devoid of scientific technicalities, and especially avoiding the jaw-breaking phrases that are worse than Greek and Hebrew to some of us, which depend on a full-blooded brain, and to which the very ingenious experiments of Durham specially apply?

Now for some of the reasons why we do not sleep. An overtaxed brain is a frequent cause. They say that the only time Gladstone went off his sleep was during his anxiety for Gordon during that anxious time at Khartoum. As a general rule, on retiring from the House after the most strenuous debates, he invariably laid down his troubles at his bedroom door, brewed himself a cup of tea, and read for an hour or so some novel recommended by his daughter, who was his censor of the press. This seems to be rather curious—the double action of tea. Undoubtedly one often feels drowsy after drinking it; and young ladies, on returning from a ball, frequently take it to soothe their nerves, whilst, on the other hand, nothing is more certain than its irritating effect in preventing sleep. Probably the warmth of the infusion explains its soporific action, for a copious draught of almost boiling water is well known to woo the gentle goddess effectually. Some people need a nightcap of whisky, hot or cold, while

others insist on a superadded pipe; and there is no doubt that weakly people are often made to sleep soundly by being furnished with some easily digested nourishment after getting into bed. Then the room must neither be too hot or too cold, the bed must be properly placed, the weight of clothing must be carefully regulated by the temperature; chilly mortals appreciate a hot bottle, and whilst some cannot sleep with an open window, others are obliged to fling it wide before slumber can be obtained.

Heavy suppers must be avoided, and champagne in particular; either keeps people wide awake, or makes them restless, and obliged to sit up or get up, and toss about on their pillow at an unusually early hour. Of course, worry must be avoided, and it is wise not to open letters at night, lest they contain something disconcerting or depressing. Any regular noise, like a crowing cock, or a barking dog, or a squalling baby, must be suppressed, and the brain must be kept at rest as far as possible, although some people are soothed by a little reading just after turning in. Music, they say, has power to soothe the savage breast; and a good story may be recalled of one of Lord Rosebery's daughters, who was taken to task by the nurse for thinking too much after she got into bed, and who replied, "You know, I can't make my mind sit down."

It is the fashion to say that you can cure insomnia by counting up to a regulated number, or imagining sheep jumping over a gap, or some device of that kind; but I have never yet met any one who would confess to having derived benefit from these domestic expedients. So at last it comes to this, that everything else has failed and we must have recourse to narcotics; and here some important ethical questions come in. Some physicians—rather pedantically, I think—will not give their sleepless patients relief by drugs for fear they get into the habit of taking them regularly. Of course, we cannot altogether ignore this view; but Sir Lauder Brunton, the wisest and most suggestive of modern physicians, once put the case in a nutshell by saying, "Insomnia is a bad habit, and may become permanent if we do not break it."

So what are the best remedies, how should we use them, and what are the contraindications and dangers attending their use?

Now, this brings us to what is or ought to be admitted as the most difficult and delicate bit of therapeutics. To begin with, idiosyncrasy, that baffling and inexplicable individual peculiarity, introduces an element of difficulty and danger. The old saying, "What is one man's meat is another man's poison," applies still more emphatically to drugs, and we may get into great trouble if we do not "gang warily" when dealing with narcotics. For instance, a single drop of laudanum has been known to kill a baby, and yet, whilst I have seen a woman display well-marked physiological symptoms after a few 10-minim doses, I have often prescribed 20 minims of the tincture of belladonna for a child of 2 years without anything of the kind; and it is well known that a single application of the liniment will bring out a very irritating papular eruption on some skins. Certain people can take large quantities of opium without bad effects, and toleration is rapidly produced. James Payn graphically describes how he saw De Quincey toss off the best part of a glass of laudanum without the slightest inconvenience.

Then take my own case. Bromide of potassium, which so effectively soothes the nervous system and causes refreshing sleep as a general rule, even when pushed to heroic doses, has never had the slightest effect on me, and the same remark applies to the entire synthetic series, with the single exception of veronal, which cannot be used freely without unpleasant and even dangerous effects. Now, to choose our special form of drug. After all, nothing equals the rapid and eminently soothing sleep given by morphine, and its subcutaneous use not only relieves pain as by magic, but beats any other form of tonic and stimulant clean out of the field. Chloral depresses the heart, and must be used with caution, for the uncertainty of its action warns us to feel our way with great care in prescribing it, for death has been known to follow a single dose of 30 grains, and a series of cases has been recorded in which symptoms arose akin to blood poisoning, with purpuric and scorbutic eruptions, ulceration of the gums, and great prostration, ending in death; and I have known a single

moderate dose of bromide of potassium bring out the unsightly and irritating eruption of acne which is one of its most unpleasant physiological effects. The great advantage of sulphonal is that it may be continued for prolonged periods without increasing the dose. The late Sir Henry Thompson at one time took a nightly draught, which had to be very carefully prepared because of its insoluble nature; and an active and energetic friend of mine, and one of the best shots in Aberdeenshire, has taken 10 grains three times a week for many years with good effect, and has never found it necessary to go beyond that quantity; on the other hand, it is not quite free from danger, and not very long ago an elderly lady friend of mine died from evident accumulation in her system from a series of not very heavy doses taken for purely narcotic purposes.

So much for the choice of narcotics; may I say a few words about the anatomical or pathological conditions which may interfere with their action? Sleep being produced by anaemia of the brain, what is the effect of the rigidity of the arterial system in advancing years, and which, of course, prevents the rapid variation of the conditions of circulation within the cerebral mass? and what is the precise effect of pregnancy, or alcoholism, or diabetes, or glycosuria, or Bright's disease, or blood and urine loaded with uric acid, or a congested liver, or blocking of what old-fashioned writers used to call the "primae viae" by chronic constipation? Space forbids me to pursue this suggestive line further, but if the Collective Investigation Committee of the British Medical Association, which formerly did excellent work, still exists, I would recommend this subject to their earnest consideration. For, so far as I know, either there is no sufficient information to guide us or it is so scattered as to be of comparatively little use; and further contributions to our knowledge will be gratefully received and acknowledged by those who, like myself, are ignorant, perhaps through no fault of our own.

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The Morison Lectures

ON THE

PATHOLOGY OF SYPHILIS OF THE NERVOUS SYSTEM IN THE LIGHT OF MODERN RESEARCH.

DELIVERED AT THE ROYAL COLLEGE OF PHYSICIANS,
EDINBURGH, JAN. 25TH, 27TH, AND 29TH, 1909.

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LECTURE III.

I ENDEAVOURED in my last lectures to indicate some of the advances made in our knowledge of the biology and bio-chemistry of syphilis, and in this my last lecture I will try to correlate the facts with clinico-anatomical knowledge, especially in relation to the etiology of the parasyphilitic affections, tabes, and general paralysis.

PARASYPHILIS (FOURNIER); METASYPHILIS (MOEBIUS).

Parasyphilis is the term given by Fournier to those diseases of which syphilis is essentially the cause, but which are not directly the result of the syphilitic virus. Such diseases are: General paralysis, tabes dorsalis, tabo-paralysis, and primary optic atrophy. These diseases are really a single morbid entity owning the same cause; insidious in onset, progressive in character, and uninfluenced by antisiphilitic remedies. These various clinical types of parasyphilitic disease are the result of a primary neuronie dystrophy; they have a similar pathogenesis, and may occur simultaneously or successively in the same individual. In tabes dorsalis the spinal sensory protoneurons are affected; in general paralysis the cortical association neurons; in tabo-paralysis both are affected simultaneously or successively. The dystrophic process is due to a lack of durability of the neurons; it may be a slow process of decay and death of the intraspinal portion

of the sensory protoneurons, as in the case of tabes dorsalis; it may be a rapid process of decay and death of systems and communities of neurons of the brain, as in general paralysis. The former is a smouldering destruction of neural elements, the latter a conflagration often fanned into flames by microbial toxæmia, autotoxæmia, or circulatory disturbances associated with arterial anaemia and venous congestion with blood stasis of the brain. It is probable that Erb's spinal paralysis and certain cases of amyotrophic lateral sclerosis may be primary post-syphilitic dystrophies.

Fournier thus classifies parasyphilitic affections:

I. ACQUIRED SYPHILIS.

1. Acute hystero-neurasthenia of the secondary period.
2. Different neurasthenic manifestations of a more advanced stage.
3. Tabes.
4. General paralysis.
5. A special form of epilepsy.
6. A special form of muscular atrophy.

II. HEREDO-SYPHILIS.

Numerous dystrophic troubles, general or partial; malformation, notably dental; arrest or retardation of physical and intellectual development, infantilism, dwarfism, inborn lack of vitality, cachexia, marasmus, rickets, hydrocephalus, certain forms of simple meningitis in early life, possibly certain cases of true epilepsy, juvenile tabes, spinal and optic juvenile general paresis. The gravity of these affections lies in the fact that they are uninfluenced by antisiphilitic treatment. The local and general failure of development may be due (1) to the direct influence of the virus upon the life and growth of the tissues, or (2) indirectly to exhaustion of the specific energy of the cells of the central nervous system by the establishment of an altered metabolism, the bio-chemical nature of which is not yet fully understood. But, as a provisional hypothesis, we might suggest that the unloosening of lipid substances into the blood, which we know occurs in congenital syphilis, may lead to a defective *vita propria* of all the cells of the body. In some lesions of congenital syphilis it may be actually due to the local invasions and multiplication of the spirochaete, for they have been found in abundance in situations where local lesions exist—for example, the epiphysis of bone—and why not in the epiblastic enamel germs?

We might provisionally suggest as a hypothesis that in all cases of acquired and congenital syphilis the living contagium, spirochaete, excites the tissues and fluids of the body to a defensive reaction. The difference in the effects of inoculation may depend upon the virus itself. Some striking examples will be given later on which apparently indicate that there may be a special neurotoxic virus, and if such instances were more numerous we could hardly believe that coincidence could explain the facts. If, as there is reason to believe, the *Spirochaeta pallida* is the living contagium, and that, becoming generalized in the lymph and blood stream, it produces the secondary manifestations, then there is a certain amount of chance what tissues will be attacked; for the living agent, swept along in the blood stream, may become lodged anywhere, and, by blocking capillaries, cause a local focus of tissue infection. The existence of a generalized eruption implies virulence of the circulating blood, and experiments demonstrate the fact that the blood is virulent during the eruptive stage; thus, Neisser has obtained a positive result by injection of blood into the skin in the chimpanzee, and Roux and Metchnikoff have successfully inoculated a macaque monkey from the blood of the chimpanzee in the eruptive period. It would be of great interest to know how long the virulence of the blood persists after the generalized eruption, or if the consecutive attacks which may occur even after fifteen or twenty years are explained by the "contagium vivum" remaining latent in the lymphatic glands or some deep-seated organ. What is the evidence in favour of this view?

It is generally admitted that the subjects of tabes and general paralysis are recruited especially from those individuals who have had a mild attack and who very seldom show any signs or symptoms of tertiary gummatous skin, visceral or bone lesions. Fournier states: "The comparative mildness of the primary constitutional symptoms in those who ulti-