distended, there were no rose spots, and the spleen could not be felt; there were no herpes. The skin had a diffuse mottling, but no purpuric spots were seen. There was no urethral discharge. The leucocytes were 13,500 per c.cm., no alteration in a differential count of 500. The Widal reaction was not present. At 10 P.M. the temperature had reached 106°, and he was given a bath at 80°, with ice frictions, which reduced the rectal temperature to 103°. At 11 P.M. the body seemed to be held much more stiffly. At 12 midnight he was much worse, and at 12.40 A.M. he died, about three days and three hours from the time of the initial chill.

The post-mortem examination (No. 98) showed a diffuse purulent meningitis of the hemispheres, the base much less involved and the ventricles not at all affected. The cord unfortunately was not examined. There was a recent diffuse nephritis, and the urine in the bladder contained albumen and tube casts. There was a general pneumococcus infection, no pneumonia or endocarditis, and the pneumococcus was separated in pure culture from the meningeal exudate.

THE TREATMENT OF CEREBRO-SPINAL FEVER.

In our series of cases we have used no special drugs. Morphine has been freely given to control the pain. Ice sponging has been employed whenever the temperature reached above 102.5°. Our mortality, considering that the cases were as a rule quite severe, has been low—only 8 of 18 cases in the hospital, and 9 among the 21 cases which I have seen.

I have already spoken of the possible benefits in certain cases of the relief of pressure by the withdrawal of cerebro-spinal fluid.

In two of our cases the spinal canal has been opened, drained and irrigated. Winter²⁰ in tuberculous meningitis, removed the final process of the second lumbar vertebra and drained the spinal canal. Von Ziemssen first attempted to use local therapeutics to the membranes of the cord by injecting a weak solution of iodine in a case of meningitis; and later Sahli practised permanent drainage through a cannula and catheter. So far as I know, an extensive laminectomy had not been done for acute spinal meningitis until our first case, November 6th, 1898, in which the operation was suggested and performed by Dr. Harvey W. Cushing, the first assistant in the surgical clinic of my colleague, Professor Halsted. The case has already been given in abstract under the section on Bacteriology²¹ as the one in which the staphylococci only were present at the time of operation. The spinal canal was thoroughly irrigated with salt solution and a quantity of purulent exudate washed out. No change followed in the existing paraplegia. The bladder and kidneys became infected, and he died about two months after the operation. The paraplegia persisted. At necropsy the spinal meninges were smooth and looked perfectly normal. It was impossible to say where the dura mater had been incised, and there were neither adhesions nor areas of the thickening on the pia arachnoid. There were extensive changes in the cord itself and in nerve roots.

In Case XII laminectomy was performed on the fourth day by Dr. Cushing. The patient was very ill, and the spinal symptoms were especially pronounced. A catheter was passed beneath the dura mater, and the membranes drained and irrigated with salt solution. For several days he seemed much better. He developed a hæmorrhagic cystitis and pyelonephritis, and died on the sixth day after operation.

Dr. Musser, of Philadelphia, has also had an unsuccessful case. Dr. Rolleston and Mr. Herbert Allingham have reported²² a case of sporadic cerebro-spinal meningitis, in which the patient recovered after laminectomy and drainage. On the principle of a desperate remedy for a desperate disease, the operation (which has been criticised adversely in an editorial note in the *Philadelphia Medical Journal*) seems justifiable in certain severe cases, in which, as in our first case, the spinal symptoms are very marked.

NOTE AND REFERENCES.

¹ *Public Health Reports*, vol. xiv. ² "Epidemic Cerebro-spinal Meningitis." A Report of the State Board of Health of Massachusetts, Boston, 1898. ³ *Jahr. f. Kinderheilk.*, 1891, and the *Deut. med. Woch.*, 1897. ⁴ *Loc. cit.*, p. 193. *Bull. et Mém. Soc. Méd. des Hôp. de Paris*, xv, p. 407, 1898. ⁵ The case of John Brooks (Necropsy No. 1,065) is of interest in this connection. He had an illness of eight weeks' duration, with obscure cerebral symptoms. On admission he had a urethral discharge. At necropsy there was found an extensive cerebral meningitis, with distension of the ventricles and slight meningitis of the dorsal cord. From the exudate and from the urethral discharge streptococci and staphylococci were isolated. The slight urethral secretion might readily have been overlooked, and the case regarded as a primary pyogenic meningitis. ⁶ A full report of these cases is given in the *Boston Medical and Surgical Journal*, December 20th, 1898. ⁷ *Medical News*, May 20th, 1899. ⁸ *Lancet*, 1895. ⁹ *American Textbook of Medicine*, vol. 1, p. 163. ¹⁰ *Johns Hopkins Hospital Bulletin*, 1897. ¹¹ *Montreal Medical Journal*, March, 1898. ¹² *Journal of Pathology and*

Bacteriology, vol. v, 1898. ¹³ *The Morbid Anatomy of Pneumonia*, *Canada Medical and Surgical Journal*, May, 1885; and the Gulstonian Lectures on Malignant Endocarditis, *BRITISH MEDICAL JOURNAL*, 1885, i; ¹⁴ *Deut. Arch. f. klin. Med.*, Bd. xxix. ¹⁵ *Arch. Gén. de Méd.*, 1887. ¹⁶ Nothnagel's *Specielle Pathologie und Therapie*, Bd. xiv. ¹⁷ *Arch. Gén. de Méd.*, 1887, i, p. 273. ¹⁸ *Twentieth Century Practice*, vol. xvi, p. 193. ¹⁹ *Lancet*, 1897. ²⁰ *Lancet*, 1899. ²¹ And reported in *Boston Medical and Surgical Journal*, December 29th, 1898. ²² *Lancet*, 1899.

THE CROONIAN LECTURES

ON

SOME POINTS CONNECTED WITH SLEEP, SLEEPLESSNESS, AND HYPNOTICS.

Delivered before the Royal College of Physicians of London.

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LECTURE I.

WHEN the late President did me the great honour of asking me to deliver the Croonian Lectures for 1899, I felt some diffidence in accepting the invitation; but on thinking the matter over it occurred to me that some points connected with sleep, sleeplessness, and hypnotics, which had engaged my attention, might possibly be of sufficient interest to bring before the College. Let me therefore thank the College for the task which was entrusted to me, and ask you to consider with me, in the first place, the

PHYSIOLOGY OF SLEEP.

For a long time sleep has been viewed from two standpoints—the physiological and the psychological—and although an attempt to combine the two is sometimes observed, they have remained distinct to the present day; for, notwithstanding the great development of physiological psychology, little has yet been done to bridge over the great gulf between the two sciences. But the question of the correlation of physiology and psychology may yet be solved, and the solution is necessary for a true conception of the phenomena of sleep.

On the basis of recent discoveries in the physiology, and more particularly in the histology, of the nervous system, various theories of the causation of sleep have been advanced; but before we can consider these in detail it is necessary to review our present conception of the central nervous system.

The view now current is based upon Waldeyer's idea of a nervous system made up of independent elements—neurons and other cells—intimately and complexly arranged. Each neuron consists of a cell body with branching processes (dendrons or dendrites) and an axis cylinder process (axon or axite). The dendrons springing from various parts of the cell body divide and subdivide until extremely fine terminal processes (dendrites) are reached, which end apparently freely in a homogeneous matrix. In many cases upon the dendrites short lateral offshoots termed gemmules or thorns may be seen, and occasionally, especially in the young, nodosities may also be noted. The axon, contrary to former belief, is known to give off branches or collaterals, which again subdivide among the dendritic processes of other cells or form a network around their bodies. In no case, however, is there believed to be direct continuity. Each neuron is an independent unit, and as such comparable with the cells forming other organs of the body. The supposed mode of combination of the various nerve cells is shown in the diagram on p. 1528, col. 1, taken from Ramón y Cajal's Croonian Lecture.

The neurons, as might be expected, vary in the different parts of the brain and cord, both in regard to the size, form, and intimate structure of the cell body, and to the form and branching of its processes. But our immediate purpose is rather with the function than with the size and form of the cell. Those anatomical features that are concerned with the function of the cell are alone in the present connection of interest, and latterly they have received considerable attention. It is said that the fibrils of the axon process can be traced in some cells into the dendrons, and it has been stated that the function of the cell body, in such cases, is purely nutritive. Generally in the cell body a granular formation, more or less definitely arranged, is observed, the granules around the nucleus being more or less spherical, those at the periphery more elongated. These granules are believed to be connected with the functional activity of the cell; they disappear, for example, from the cells of the cervical ganglion after long-continued electrical stimulation (Vas, Lambert, Hodge), and the cells of the cerebral cortex, even when affected by ordinary stimuli, show a diminution in their staining power when compared with unstimulated cells (Mann, Lugaro, Demoor). Changes in the form and volume of the cell have also been described. With moderate activity, turgescence of the cell and nucleus and accumulation of chromatin particles occurs, and after prolonged work shrinking of the protoplasm and irregularities in the contour of the cell and the nucleus are observed.

All physiologists who accept Waldeyer's view believe that the transmission of nerve impulses occurs through the intercalated material between the terminal cell processes, but

some doubt has been thrown on the isolated character of the neurons. Our present conception of the nervous system is due almost entirely to investigations with Golgi's silver method; but Dr. Alex Hill, in his presidential address before the Neurological Society of London (1896) has raised objections against the trustworthiness of this method in proving the presence or absence of continuity of the processes of different cells; and I am inclined to agree with these objections; yet apart from the observations of Golgi, Waldeyer, Ramón y Cajal, van Gehuchten, and others, my greatest difficulty in accepting the continuous nerve-fibril theory is an *a priori* one. It is that of the cellular constitution of tissues. The various

The principal types of cells of the cerebral cortex of the mammifera: A, pyramidal cell of medium size; B, pyramidal giant cell; C, polymorphous cell; D, cell of which the axis cylinder is ascending; E, cell of Golgi; F, cell peculiar to the molecular layer; G, fibre ending freely in the substance of the cortex; H, white matter; I, collateral of the white matter. (After Ramón y Cajal.)

neurons are merely modified cells, the processes of which have their birth in the body at some period of embryonic life. According to present views these processes usually grow to a remarkable fineness, and closely approximate, but without uniting. If they unite, what is the cause of their union? It is almost as difficult to accept the idea of the coalescence of these individual dendritic processes as it is to understand the transmission of impulses between isolated cells.

The thorns, or, as they are more frequently called, gemmules, are short lateral protoplasmic extensions of the final dendritic processes of the neurons. They are most marked on the dendrites of the large pyramidal and Purkinje's cells, and they appear to end in a rounded knob-like extremity. But do they end thus? Hill believes that this appearance is

purely an artifact, and due to the spread of the neuroplasm along the fibrils after death. The thorns, he thinks, indicate an actual union between certain unstained filaments and the protoplasmic processes.

Another theory of the function of these gemmules and the transmission of impulses has been put forward by Berkley. He accepts the knob-like terminations of the gemmules as natural, but he cannot accept Cajal's theory that nervous forces may discharge themselves from axites to dendrites all along the line. The dendrites, he believes, are covered with a thin enveloping sheath through which the gemmules penetrate, and it is only at the tip of the gemmules that naked protoplasm exists. Similarly the fine branches of the axites are covered with "a protective sheath of great tenuity," and only exhibit naked protoplasm at their bulbous terminations. Therefore Berkley believes that it is only between these free terminations that nerve impulses can pass.

The mode of branching of the axites varies according as they form ascending fibres (extrinsic) or belong to local cells (intrinsic). The extrinsic break up into a number of filaments, usually at some distance from one another, which subdivide. These course over a short extent of territory, and terminate in flattened or globular extremities, the number seldom exceeding 6 or 8 (Fig. 2).

Fig. 1. Psychological neuron, showing the end apparatus of a collateral situated against the dendrite of another cell; human. Fig. 2. Form of termination of the ascending fibres of the cortex; guinea-pig. (After Berkley.)

The terminations from the collaterals of the psychological cells show a very different disposition. Winding among the dendrites of the cells, and often closely applied to them, they seldom show any definite endings until the mid-portion of the layer of small pyramidal cells is reached. There they split up into a number of exceedingly fine branches, which frequently run parallel with the course pursued by the apical and basal dendrites. They eventually give off at frequent intervals exceedingly short collaterals usually from the side nearest to the dendrites, which terminate in a round or flattened bulb-like extremity similar to those on the branches of the ascending fibres. These are closely applied to the bulbous tip of the gemmules, the appearance often suggesting one of actual contact, the axonal discharges of the stimuli overleaping the infinitesimal distance between the bulb and gemmule (Fig. 1).

"The interpretation of the objective existence of the terminal apparatus of the nerve fibres," Berkley says, "cannot be made but in one way—namely, that the impression conveyed from external sources to central cell, and from local cell to local cell, is not accomplished by a diffusion of the excitation through the whole cortex, or even at various points along the course of the finer branches of the axons, but at single points—perfectly definite in their distribution, and that these points are situated only at the extremities of the nerve fibre twigs in the form of a histologically exact formation—the bulbous ending of the nerve fibre—which in itself constitutes the sole and only means for the carrying over of the cellular forces from axon to dendron and from cell to cell. This is in entire conformity with the conception of Waldeyer of the entity of the neuron, each cell standing as a unit in the nervous formation and only in continuity with others at definite points." In a still more recent communication Lugaro also states that the transmission of impulses occurs through the extremity of the gemmules. The he believes are capable

of expansion and retraction to a slight degree, and upon this function he bases his theory, which I shall presently allude to, of psychical processes. A form of nerve termination in the central nervous system has been described by Aldren Turner and Hunter in the spring number of *Brain* for 1899; but so far this has not been utilised to explain sleep. After injecting methylene blue into the circulation during life, they found after death a fine lattice-work arrangement over the cells in most parts of the brain. This was most marked over the root of the axis-cylinder process, and according to these authors it is the termination of the axis-cylinder of another cell. There is no continuity of tissue, and therefore the entity of the neuron is not questioned. Nerve impulses are believed to pass from the network to the cell body and not from terminal axite to dendrite or *vice versa*. The function of the dendritic processes, the authors are inclined to believe, is nutritive, a theory first suggested by Golgi.

After this brief survey of the place of the neuron in nerve physiology we shall be better able to understand some of the theories which have been put forward to explain sleep. But before dealing with these it will be well to review the facts which it is necessary to explain.

Speaking generally, during sleep the metabolism of the body is lowered. The respirations are shallower, the aëration of the blood is less active, the pulse is less frequent, the blood pressure is lower and the temperature tends to fall, the nervous system is so affected that sense stimuli of moderate intensity are not perceived, consciousness is in abeyance, but reflex effects can still be obtained. These phenomena are not constant during the sleeping state, but vary within fairly wide limits. On this account some of them have been credited with an etiological rôle, and this leads us on to the

THEORIES OF SLEEP.

Those advanced up to the present time may be divided into chemical, histological, vasomotorial, and psychological. Let us first consider the cause of sleep in the abstract. It is evident that consciousness, whatever this may be, is due to a definite condition of the nerve cells or neurons, and any departure from complete consciousness must be due to some change from this state. At the present time it is difficult to come to any other conclusion than that this state and its alterations are of a chemical nature; that consciousness is accompanied by, if not due to, a normal metabolism of the nervous cells, and unconsciousness or diminished consciousness to an alteration in this metabolism. This so-called normal metabolism is the result not merely of the vital requirements of the cells, but of this *plus* the alterations produced by the inflow of stimuli. Diminish the stimuli or make them constant both as to kind and intensity (monotony), and the metabolism may become constant though in changed conditions; a kind of rapid acclimatisation occurs, and with it diminished consciousness. The same effect might be produced by the alteration of metabolism due to the application of a poison.

It seems to me that the fundamental phenomena to be determined in dealing with psychical processes are the chemical changes occurring in the cells; molecular vibration and processes of a similar nature, which have been speculated upon from time to time are, with our present knowledge, in the realms of the unknown. Even if they can be known it seems more philosophical to determine the gross chemical changes first, although there is not much likelihood of these being actually demonstrated in the near future.

Admitting that chemical alterations are the causes or proportional concomitants of states of consciousness, we shall be able to trace a connection in some of the various theories of sleep which have been propounded. Thus it is very evident that the metabolism of the cerebral cell may be, and probably will be, altered by changed extrinsic conditions—for example, by the blood supply—and that it may produce gross physical changes in the cell—for example, retraction of the protoplasmic processes. The vasomotorial and histological, and in part the chemical theories, may be thus brought into connection; but let us examine the theories in detail.

The most fascinating of them all is what Duval has termed the histological theory of sleep. This seems to have been propounded in its most rudimentary state by Rabi-Rückhard, who suggested that an assumed amoeboid motion of the neurons, and especially the dendritic processes would account for various psychological phenomena. Thus sleep might be explained by a retraction of these processes and consequent inability of nervous impulses to pass from one neuron to another. The same theory was elaborated independently by Lépine and Duval. Lépine thinks this isolation of the indi-

vidual neurons may be due to some chemical modification of the cellular protoplasm, and he also states that the theory explains the extraordinary suddenness with which a state of wakefulness passes into one of sleep.

It is almost unnecessary to point out that the theory of Rabi-Rückhard, Lépine, and Duval is dependent upon the conception of isolated neurons as independent units in the composition of the nervous system, and that with the disproof of this conception their theory must fall to the ground. Kölliker has strongly criticised this (the amoeboid movement) theory. He says that Widersheim's observations on the movements occurring in the nerve cells of the supra-oesophageal ganglion of *Leptodora hyalina* are not pertinent to the question; and he rejects the comparison with the action of curare as irrelevant. Widersheim did not observe movement in the processes of the cells; and in the transparent parts of living animals, where nerve terminations have been observed, no movement has been perceived. Moreover, he thinks that if amoeboid movements occur, physical conditions would tend to act in a constant manner, and the same mental states under varying conditions would be impossible. Furthermore, he says that "it cannot be doubted that the essential function of the nervous system—that is, psychical processes—is bound up with the nerve cells."

In many of his criticisms he seems to me to lay too much stress upon the stability of the axis-cylinder process. The structure of this can hardly be compared with that of the more delicate dendritic processes; and stimuli, without influencing the former, might powerfully affect the latter. At the end of his paper he expounds his theory of psychical conditions, a theory with which we have long been familiar. He advocates the view that facility in thought and action is due to diminished resistance in the pathways, but in what way this occurs he does not state.

Rámon y Cajal strengthens Kölliker's objections by the following: (1) The nerve terminations of the cerebellum, the olfactory bulb, the central auditory ganglion, and the optic lobe constantly show the same extension, form and degree of approximation to the cell bodies, whatever may have been the mode of death of the animal (hæmorrhage, chloroform, curare, strychnine, etc.). (2) The nerve terminations of the retina and optic lobule of reptiles and batrachians (the animals on which he experimented) show the same condition, whether the organ was hardened after continued rest as after long retention in the dark, or after activity, as when it had been kept several hours in the sun. He therefore believes that the axites and dendrites possess a constant disposition. But in order to explain sleep and other physical phenomena he brings in another factor. Under different conditions, he found the processes of the neuroglial cells contracted or expanded, and he suggests that a function of these cells is to act as an isolating medium between the neurons. During sleep the neuroglial processes are introduced between the nerve ramifications and the cells or their protoplasmic processes, in consequence of which the passage of impulses is prevented or hindered. Apart from the seat of operation, Cajal's theory differs from Duval's in that the processes (neuroglia in the case of Cajal) are expanded when the brain is at rest and are contracted when in action. The contraction is usually automatic, but may be brought about by the action of the will. I do not, however, propose to follow Rámon y Cajal in his explanation of psychological phenomena on this theory, especially as his observations have not been confirmed by more recent investigators. His theory seems to me to endow the neuroglial cells with more nervous activity than they are capable of, and to allot to them a function which, from their position and structure, I venture to think improbable. Moreover, if we accept the network theory of Boll, Hill, and others, or Berkley's or Lugaro's modification of the usually-accepted view, this explanation loses nearly all its significance.

Before leaving the histological theories of sleep, I will briefly refer to a view recently advanced by Gotch to explain the conditions of hypnotism. He goes further than Duval in attributing a major influence to the periphery of the neuron, for he believes that the gaps between the terminations of the adjoining dendritic processes are of primary importance in the transmission of nerve impulses. These gaps determine whether an impulse shall pass or not; once it has passed

Gotch believes nothing can hinder its further course. The gaps are capable of variation; in fact, he states that: "the whole of modern physiology is inexplicable except on the supposition that the gaps are susceptible of alteration. What this alteration is we do not know; the gap consists of living tissue, and, like all living structures, is constantly undergoing molecular change." The resistance of the gap varies with different conditions; thus the action of the higher nerve centres increases the resistance, the force of habit or practice diminishes it; constant attention leads to fatigue changes in the intercalated material, and the forcing of the gaps is then "a concomitant of the mental mood of volitional attention."

Although this theory is primarily advanced to explain hypnotic phenomena, it is evident that a similar explanation might be advanced to account for sleep. It does not seem quite clear to me whether the resistance is due to a molecular rearrangement of the intercalated material or to an increase of its amount between the dendrites. If the latter, as is suggested in one place, the conditions simulate those advanced by Rabi-Rückhard, Lépine, and Duval. Gotch's theory differs from theirs in attributing a greater influence to the gaps than to the protoplasmic processes. Like its allies, it must consequently stand or fall with the proof or disproof of the neuroniconception of the nervous system. To me it seems to attribute much too active a function to what one has already been taught to regard as a passive structure; but past teachings must avail little if the present ones are sufficiently convincing; to me they are not.

The most recent theory has been advanced by Lugaro. According to him unconsciousness is not due to a retraction of the terminal dendritic processes, but to an expansion. As I have already said, he believes that nerve impulses pass through the gemmules, and that the passage is facilitated or inhibited by the closer or remoter relation of these to each other. During ordinary thought but few of these are in contiguity, the others are retracted. The latter are in a potential state, that is, they are capable of being approximated by any suitable stimulus. Lugaro's theory differs from that of Lépine and Duval in that expansion of the gemmules is regarded as the resting phase, and contraction as the active one. Thus in sleep the gemmules are believed to be expanded, the paths for impulses are thus enormously increased, and this leads to confusion of thought and loss of consciousness.

In the unsettled state of the views of neurologists on the structure of the nervous system, it would be impertinent to criticise these histological theories in detail; further research alone can settle present conflicting opinion, and on the result of this depends the probability or possibility of the minute changes we have considered affording an explanation of psychical phenomena.

The vasomotor theory of sleep is almost as popular as the histological theories, and interest in it has recently been awakened by the experiments of Professor Howell, of the Johns Hopkins University. It has, however, been a favourite theory for many years. Based upon direct observation of the cerebral cortex by Donders, Durham, Hammond, and others, and on the plethysmographic researches of Mosso, it seemed to possess a firm foundation, but of late this has been rudely shaken. The conditions of experimentation in these researches were not normal, and further investigations have shown the necessity of modifying our views on the matter. Thus Mr. Leonard Hill has proved that practically no change occurs in the cranial contents, that the brain at nearly all points is in contact with the cranial wall, and that the amount of cerebro-spinal fluid in the intact cavity is very small and incapable of gravitating to any appreciable extent into the spinal canal. Moreover, he has shown that the cerebro-spinal pressure equals the venous pressure, that it does not rise beyond it, and that the cerebro-spinal fluid does not normally function as a compensating mechanism for alterations in the cranial contents. "The volume of the blood in the brain is in all physiological conditions but slightly variable." Therefore, cerebral anæmia, if we regard this as a diminution in the total quantity of blood in the brain, cannot exist to any extent. It is possible for an arterial anæmia, combined with venous congestion to occur, and Hughlings Jackson's observations on the retinal vessels during sleep would render this not improbable. In view of Leonard Hill's researches it seems absolutely necessary to recognise the Munro-Kellie doctrine (the incompressibility of the brain and constant volume of the cerebral contents) in dealing with the causal factors of sleep.

Cappie, on purely theoretical grounds, advocated this doctrine, and advanced a theory of sleep in harmony with it. The main feature of his view is, that the arterial anæmia of the brain is compensated by a filling of the pial vessels, and an alteration of the normal pressure on the cerebral surface from an expansive to a compressive force.

Since Leonard Hill's investigations, Professor Howell has advanced a modified form of the vasomotor theory based upon personal experiments. According to him, the anæmia of the cortex is counterbalanced by the dilatation of the vessels at the base of the brain. The causal factor of sleep is a fatigue of the vasomotor centre, and particularly of that part of it supplying the skin area. This Howell deduces from the fact that the volume of the arm increases (that is, the cutaneous blood vessels dilate) just previous to sleep, and it usually contracts suddenly on awaking. He does not, however, ascribe the production of sleep solely to the fall of blood pressure, but he regards this as pre-eminent. The etiological factors he gives as:

1. A diminution of irritability caused by fatigue of large portions of the cortical area.
2. Voluntary withdrawal of sensory and mental stimuli involved in the preparations for sleep.
3. A diminished blood supply to the brain, owing to a relaxation of tone in the vasomotor centres, and the fall of general arterial pressure thereby produced.

Recently Leonard Hill has criticised Howell's results or rather his deductions from his results. He finds that the fall of arterial pressure is concomitant with sleep, and he adduces confirmatory experiments. Thus he found arterial pressure "as low when lying in bed in the waking state in the morning as in the sleepy state in the evening," a result evidently antagonistic to Howell's theory. Moreover, it is not difficult to explain the fall of blood pressure during sleep, or even previous to sleep, by the posture, diminution of external stimuli, extra clothing, etc., which we seek before endeavouring to sleep. The rapid rise of blood pressure at the moment of awaking Leonard Hill explains thus: "As the waking state is neared the turgescence of the limbs is lessened owing to the increased tone of the muscles and to the restlessness of the sleeper. Each movement or deep respiration expresses the blood and produces a lessening in the volume of the arm. This is shown to be so by an examination of Howell's tracings. Since each movement of the body momentarily raises the vena cava pressure, the brain is congested thereby, for the cerebral circulation passively follows every change in vena-cava pressure. The flushing of the brain is secondary to the external stimuli which provoke the external movements of the body, accelerate the heart, and increase the vasomotor tone. At the same time these stimuli may awake the dormant consciousness. Carefully reviewing all the above facts we must, I think, conclude that the anæmia of the brain is caused by rest of the body and the cessation of powerful objective and subjective stimuli. It is the cessation of the latter that produces sleep."

As regards the fall of arterial pressure being *post* or *propter*, I agree with Leonard Hill that it is the former. The vasomotor theory of sleep is quite inadequate to explain this condition; nevertheless, vascular phenomena play a part, and an important part, in sleep production. What, then, is the probable condition of the cerebral vessels in sleep? We have seen that the brain is a closed cavity, that the general arterial pressure falls during sleep, and that the pressure in the intracranial veins varies absolutely with that of the intrathoracic venous pressure; and it may be further stated that the intracerebral blood vessels have not been shown to possess any vasomotor innervation. It follows from these and other facts that the arteriole pressure is dependent on the venous pressure, and that any diminution in the size of the arterioles must be replaced by increase in size of the veins or other cerebral vessels. Howell believes the basal vessels dilate, but I am more inclined to agree with Cappie, who attributes the greater action to the pial vessels; probably both sets of vessels are involved.

But the condition during sleep, it seems to me, is rather one of comparative blood stasis than of simple anæmia. In either case a small amount of blood passes through the cerebral vessels in a given interval of time, and this is in reality the essential factor. And although I cannot regard a fall in blood pressure as the primary causal factor of sleep, yet the diminished supply of nutriment thus produced must exert a depressing influence on the metabolism of the cerebral cells, and aid in sustaining, if not in inducing, sleep. That the fall of arterial pressure is not necessary is shown by the action of many hypnotics, which directly exert no influence in this direction; but it may also be said that, other things being fairly equal, those hypnotics which depress blood pressure are more certain sleep producers than those which do not. Chloral, for example, is more certain than any of its derivatives.

The admissibility of pharmacological evidence naturally raises the question as to whether forced sleep from drugs is comparable to natural sleep. Although some hold to the contrary, I am inclined to believe that it is. The restorative effect of a properly apportioned dose of a hypnotic in mild cases of insomnia is suggestive. Moreover, if we accept the idea that sleep is the result of chemical changes in the cerebral cells, this conception gains in force, as the introduction of a hypnotic into the organism merely means a change in the environment of the cell, with subsequent variation in its activity. To deduce from the narcosis produced by large doses of these drugs that artificially produced and natural sleep are dissimilar is unfair; in this case the stimulus is excessive, and the result not comparable. But to return to the theories of sleep.

The various chemical theories which have been put forward seem to have been based on insufficient data. With the older theories of Sommer and Pfüger and others, I do not intend to deal. But comparatively recently a new chemical theory has been advanced. Errera believes that the leucomaines produced by the normal activity of the body play a predominant part. He has based his view mainly on the experiments of Bouchard and his school, who found that during the night convulsant substances were excreted in the urine, which were not present during the day. The toxicity of the urine during sleep was found to be much less than that passed whilst awake. On these experiments Bouchard formulated the theory that during the day the body formed a hypnotic substance which, by its accumulation, produced sleep, and that during sleep a convulsant substance was formed which by inducing muscular movements produced awakening. Both Beck and Herringham have failed to corroborate Bouchard's experiments, but apart from this it is difficult, from evidence of this kind, to draw conclusions as to the cause of sleep. The urine is a complex body, it varies largely in composition with the kind of food, the amount of exercise, and other physiological and pathological conditions, and this variation is greater with it than with other secretions. It does not seem right to compare the variability of the composition of the urine with the periodic alterations in the temperature and pulse; the limits of the first are much wider. Furthermore, as in the case of blood pressure, it does not seem to me proved that this altered composition of the urine is not *post* rather than *propter*. I do not mean to imply that metabolic changes have no influence in the production of sleep, but what I do maintain is that sleep has not been proved to be due to any one substance, or group of substances, present in the urine. The chemical theory from another point of view I shall mention presently.

The fourth class of our division of the theories of sleep is the psychological. And here we enter upon difficult ground. We have seen that the physiological and psychological are two separate spheres with independent methods of analysis; that the elements of the two sciences are different, and that the connection between the two can only be one of parallelism. It may be that we shall never get beyond this stage; but from a physiological point of view there seems nothing improbable in the idea that they may be correlated. Marie de Manacéine, in a popular book on sleep published two years ago, defines sleep as "the resting time of consciousness," and perhaps from a psychological point of view no better definition could be given, but to me it is a mere statement of a psychological fact, not an explanation. We cannot account for sleep in such an immaterial manner. We may not be able, perhaps, to give any further explanation at present, but the acceptance of such a theory would deprive us of that most valuable aid to research—a working hypothesis.

It is not improbable that the new schools of psychological physiology, and especially those which deal with it from the pharmacological side, may help us to a truer conception of the causes of sleep. Wundt and his pupils have already added something in this direction, and it is especially to his pupil Kraepelin that much of our knowledge in this department is due.

In a recent paper from his laboratory a new explanation of the action of hypnotics is given. Working on the psychical influence of trional with Kraepelin's methods, Hans Haenel found it to diminish the power of calculating and learning by heart, to increase the time in the choice-reaction, to diminish the erroneous reactions, to increase faults and omissions in reading and apprehension, and to diminish the rapidity of writing. He found it, however, to exert no influence on association and muscular work (ergographic curves) nor on the rapidity of repeating things pre-

viously learnt. The hypnotic action of the drug is explained, Haenel says, by the depression of apprehension and the increased difficulty in originating co-ordinate movements. He draws attention to the fact that these, and especially diminished power of apprehension, are present after all hypnotic drugs have been given, and the fact that morphine is not regarded as a hypnotic in small doses is due to the stimulant rather than the depressing effect this exerts on psychical processes. This in psychological terms is the condition produced by the action of hypnotics, but as an explanation of sleep it is not sufficient.

If, then, we feel obliged to discard psychological explanations, and with due deference we must do this, we can only return to physical and biological science. As we have said, the fundamental changes must be in the neurons themselves. I am inclined to believe that these are primarily of a chemical character; the differences observed between rest and activity and the changes resulting from the administration of various poisons, I think, support this view. But these differences are in no sense crucial. Before we could consider them such it would be necessary to know for certain what cells are concerned in the production of mental phenomena, and what changes result from the action of hypnotic drugs upon them. The action of poisons on nerve cells generally is, however, at least suggestive, as it shows that marked changes of a more or less transient character may occur during life.

Many years ago (1876) W. Ludwig, a pupil of Binz, described changes in the nerve cells of excised and teased cerebral tissue after the application of hypnotics. A year later Binz himself described the effect of morphine on isolated nerve cells. More recently the action of poisons has been investigated by means of Nissl's method, and a great number, including many metals, alkaloids, and toxins, have been found to produce distinct changes. Nissl believes that this action is characteristic for the same poison and the same kind of cell, but as yet there is a want of unanimity on this point. That decided morphological changes may be produced by the action of poisons all are agreed, and that these changes may be rapidly produced has been shown by Goldscheider and Flatau in some recent interesting researches.

Changes, too, are produced in the dendritic terminations of the cells, and usually these appear earlier and are more marked than those in the cell body. But in the dendrites more than in the cell observers differ as to the exact conditions present. Thus, after the administration of morphine, Demoor describes nodosities on the dendrites, which in extreme cases are reduced to mere moniliform filaments, while Lugaro observed expansion of the gemmules and very slight thickening of the processes. Alterations of the dendrites have been noticed by various observers after hypnotic drugs, and there can be little doubt that transmission of nerve impulses through these must thereby be markedly retarded, if not prevented.

Owing to the difference of opinion of observers regarding the exact condition produced by hypnotic drugs, it is impossible to draw a satisfactory conclusion regarding their mode of action or the cause of sleep. I am inclined to believe that hypnotics act chemically upon the neurons, both upon the cell bodies and their dendrites, and I think histological observations support this view. Retraction of the terminal processes or gemmules, if such occur, I believe to be secondary. But what part is played by the cell body, and what by the terminal processes, it is difficult to say. The finer dendrites are probably more exposed to external influences, and any modifications in them must affect the transmission of nerve impulses, but the cell body is the seat of metabolic activity, and this too must be readily affected by changes in the environment. Lugaro's view of the action of hypnotics and the cause of sleep I have already noticed. Demoor, as a result of his histological researches, desists from any attempt to formulate a theory of sleep.

Turning now to the more immediate object of these lectures, I intend to deal with the class of hypnotics in a very general manner. The next two lectures will be devoted purely to pharmacological matters; in the last I propose to deal with the rational treatment of insomnia. The pharmacology will not, however, be solely concerned with the hypnotic influence of the drugs. I intend to take a much broader view and extend my thoughts to substances, which, although they possess no value as medicaments, yet are of considerable pharmacological interest. As the tendency for many years past has been towards a chemical view of pharmacological actions, I shall as far as possible take up this line. I propose first to deal with the hypnotics of the fatty series, and afterwards with those obtained from the vegetable kingdom.

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CASE OF MULTIPLE ADENOMATA OF THE SKIN.

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THE patient, G. E., aged 43, is one of a family of three. She has had two children; one died aged two years, and the other is now 24 years of age, and in neither, or in any other relative, has there been any manifestation of the mother's disease. The patient came to the Blackburn and East Lancashire Infirmary in October, 1897, and asked to have some lumps removed from her head as they were rather unsightly and prevented her wearing a hat comfortably. She stated that thirteen years previously she noticed some small lumps growing on her forehead, scalp, and ears. They gave no pain, but had gone on increasing in size and number

Multiple Adenomata of Skin.

till there were quite thirty scattered over the forehead, scalp, and ears. There were a few very small ones scattered over the trunk. The largest was 2 inches long and 1 inch wide, and projected from the scalp about 1 inch. It, like many of the others, was slightly pedunculated. The skin over it was hairless and apparently atrophied, being smooth and shining, and having a few enlarged blood vessels coursing over its surface. The other tumours were more rounded than this, which seemed to have been formed by the fusion of two masses originally separate. The tumours varied in size from mere papules to large cherries, and although most were slightly pedunculated, were quite

immovable in the scalp. They were, however, not attached to the underlying bone in any way. One on the right temple was shaped like a mushroom with a very short stem, the shape being no doubt produced by the pressure of the head on the pillow during sleep. The tumours felt solid, and were quite painless.

A day or two after admission to the infirmary about a dozen of the more prominent tumours were excised by Mr. Hunt. They had to be dissected off the pericranium. There was free bleeding for a few minutes but it stopped when the sutures were tightened.

On section the tumours looked like fibrous tissue to the naked eye, but under the microscope the appearances were, I think, rather unusual. The section shows masses of epithelioid cells arranged very regularly in a fibrous tissue stroma, the whole surrounded by a thin connective tissue capsule. These masses vary in shape but are for the most part round or oval; here and there they are cylindrical, or more irregular in shape, this, no doubt, depending on the direction of the section. The cells at the periphery of these masses are arranged in columnar fashion. The cells are for the most part round or oval, and their large nuclei stain readily.

Section of Tumour.

Clinically the tumours are certainly not malignant. There has never been any tendency to ulceration in any of them. A case, apparently of a similar nature, is recorded by Dr. James W. Barrett and Dr. Percy Webster, of Melbourne, in the *BRITISH MEDICAL JOURNAL* of February 6th, 1892. They call their case one of "Multiple Sudoriparous Adenomata of the Scalp." Mr. Jonathan Hutchinson, sen., in his *Archives*, vol. vi, No. 21, Plate cxix, illustrates this case, but limits the name to "tumours of the scalp." The photograph of the patient was taken six months after she was first seen, and the tumours now noticed are distinctly but very little larger than they were then.

I am indebted to Mr. Hunt for permission to publish the case.

ITALIAN LARYNGOLOGICAL SOCIETY.—The Italian Society of Laryngology, Otology, and Rhinology will hold its fourth general meeting in Rome in October of the present year, under the presidency of Professor Giuseppe Gradenigo of Turin. The subjects proposed for discussion are: (1) The paths and modes of diffusion of tympano-mastoid infection (to be introduced by Professor Camillo Poli of Genoa; (2) the physiopathology of the olfactory nerves (to be introduced by Professor Vittorio Grazzi of Pisa); and (3) parasymphilitic or postsyphilitic lesions of the larynx. The following question will also be proposed for discussion: The Title of Specialist in Oto-rhino-laryngology.