ON THE PARALLELISM BETWEEN THE THREE THERMIC MECHANISMS AND DR. HUGHLINGS JACKSON'S THREE LEVELS.

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In his Lumleian Lectures, which have recently appeared in the JOURNAL, Dr. Hughlings Jackson refers to his oft suggested hypothesis that there are three levels of the central nervous system. The lowest, or first level, consists of the cord, medulla, and pons; it is the first evolved, and represents the simplest movements of all parts of the body. The middle, or second level, is composed of the Rolandic motor area and the corpus striatum; it is the next evolved, and represents complex movements. The highest, or third level, is made up of the centres of the prefrontal lobes; it is the last evolved, and represents the most complex movements. There are three classes of fits corresponding to discharging lesions of each of these levels. Each of these levels is sensory as well as motor, hence they are called sensori-motor levels. I have been accustomed to point out that there are also three thermic levels of the cerebral nervous system.

I need not now refer to the reasons for and against this view as they are summarised in an article on the "Theory of Pyrexia" in the current number of the *International Journal of Medical Sciences*, but my object here is to show that the hypothesis of three evolutionary sensori-motor levels and the modern theory of the temperature-regulating mechanism mutually support one another, for in each the number of levels is the same, their anatomical position is the same, they vary equally in complexity, and their order of evolution is similar.

The heat mechanism consists of three parts. First, a heat loss or thermolytic mechanism, consisting of the cutaneous vessels presided over by the vasomotor nerves, the sweat glands, presided over by the sudoriparous nerves, and the respiratory movements, controlled by various nerves. It is well known that the vasomotor, sudorific, and respiratory centres are in the medulla and cord. The thermolytic mechanism is the earliest developed, for most animals lower in the scale than birds have no other heat mechanism; they are cold blooded, their temperature for the most part rising and falling with that of the external medium; the only means they have of regulating their temperature is the very simple one of modifying the rate of loss. The early development of this mechanism is also seen in the fact that, during all but the latest months of pregnancy, the human child is practically cold blooded, for prematurely born infants can only be kept at a natural temperature by external artificial warmth. Lastly, that the thermolytic mechanism is the most fixed, and therefore the earliest developed, is also shown by the fact that it is difficult to influence it, as we see in the circumstance that the fall of temperature produced by sudorifics is slight and uncertain. The central thermolytic mechanism, therefore, corresponds to Hughlings Jackson's first level.

The second part of the heat mechanism is the thermogenetic or heat producing. Most of the heat formed within the body is developed by chemical changes going on in the muscles apart altogether from their motor properties, and this thermogenetic function is presided over by the corpus striatum, for irritation of that body, either by artificial experiment or disease, results in such a considerable rise of temperature that it must be due to an increased production of heat, which increase is actually proved by calorimetric measurements. The corpus striatum is part of Dr. Hughlings Jackson's second level, and it ought really to be looked upon as a portion of the cortex, for not only is it continuous with the cortex at the base of the brain, but it is developmentally part of it. A heat-producing mechanism is clearly more complex than a simple thermolytic mechanism. Evolutionarily the thermogenetic mechanism is evolved next to the thermolytic, for it must appear before the thermotaxic, which adjusts the balance between the other two. This order of evolution is confirmed by the fact that fish and amphibians have small corpora striata; in reptiles, some of which, as the python, are warm blooded, these bodies are larger; whilst in birds, which produce much heat, they are very large. The thermogenetic function not having been fixed so long as the thermolytic is more easily influenced by drugs, as we see in action of antipyrin and antifebrin, which it has been shown will not act if the corpora striata are destroyed. It is interesting

to notice that in tetanus and hydrophobia, in both of which there is a considerable rise of temperature, there is also a long continuance of motor fits, due in part probably to disturbance of the lowest level, judging not only from the character of the convulsions, but also from the fact that in hydrophobia inflammatory changes occur in the medulla, and in part to a disturbance of the second level. May not this indicate that so much of the second level is poisoned that we get both a rise of temperature and motor fits as a result of its irritation? The *post-mortem* rise of temperature in these two diseases is probably due to the continuance of the action of the poison on the thermogenetic part of the second level after the death of its motor part.

The third part of the heat mechanism is the thermotaxic, whose function is to adjust the balance between the other two. Just as the exact anatomical position of Dr. Hughlings Jackson's third level is speculative, so is the exact position of the thermotaxic centre. The rise of temperature which some observers have produced when experimenting upon the cortex near the fissure of Rolando may be due to damage of the thermotaxic centre. Ott is decidedly of opinion that it is cortical. I have recorded a case of considerable pyrexia after a cortical injury,¹ and those cases of meningitis, accompanied by hyperpyrexia, may be instances of damage to the third level of the heat mechanism. It is true that what slight evidence of locality there is rather places it over the motor area which is part of Dr. Hughlings Jackson's second level, but it must be remembered that our evidence of locality is very scanty, that the levels may overlap, and that some layers of cells in this region may belong to the second level, and others to the third. That the thermotaxic mechanism must be more complex and evolved later than the other two is self-evident. In the human adult it is fairly competent and active, as is proved by our pretty constant temperature. In the lower animals and in children it is probably not so completely evolved, for I have found that the normal temperature of rabbits varies several degrees, and rapid fluctuations of temperature are common in children, even when only slightly ill.

Being the last of the three mechanisms to be developed we should expect it to be easily put out of gear, and the great rise of temperature, so often seen towards the fatal termination of a fever, may be due to exhaustion of this mechanism, and hysterical pyrexia is probably an example of disorder of it.

We thus see that the parallelism between the three thermic levels and the three sensori-motor levels is, in their anatomy, their complexity, and their order of evolution, very close.

The accompanying diagram is to illustrate the relative positions

¹ Guy's Hospital Reports, 1884.

of the various parts of the thermic mechanism. Lesions may affect any part directly, for example, we know that hæmorrhage into the corpus striatum will cause a rise of temperature; or poisons in the blood may affect any part, most specific fevers are probably an instance of this, and we have a rise of temperature in belladonna and in fish poisoning; or lastly, it is possible that severe peripheral stimuli may influence the thermic central nervous system. Possibly instances of this last method are the rises of temperature sometimes seen in simple fractures, or in severe biliary colic, and probably the very high temperature often met with in very tense, painful abscesses, and which falls when the abscess is opened, is produced by this means.

ON OUABAIN IN WHOOPING-COUGH.

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OUABAIN is an alkaloid with the formula $C_{30}H_{46}O_{12}$, and is obtained by crystallisation from a watery extract of the roots of the ouabaïo, a plant nearly related to the *Carissa schimperi*. The juice of the ouabaïo plant is used as an arrow poison by the Somalis in East Africa.

Ouabain, its active principle, occurs in the form of rectangular crystals, which are white, transparent, colourless, and to a very slight degree bitter to the taste. It dissolves with difficulty in cold water, but much more readily in hot; it is altogether insoluble in chloroform, or ether, and but to a slight extent in absolute alcohol. Its best solvent appears to be partly concentrated alcohol, and this solubility is increased by heat.

Professor Gley and M. Arnaud, both of Paris, first studied the physiological effects of ouabain in frogs, rabbits, and dogs, and they found that in a frog $\frac{1}{1000}$ grain caused death by arresting the heart's action. In a dog, $\frac{1}{10}$ grain produced marked slowing of the respirations, without much cardiac disturbance; $\frac{1}{100}$ grain first stimulated, and then slowed respiration, until it ceased completely. Subcutaneously the drug was found to act much more powerfully than when given by the stomach; and $\frac{1}{10}$ grain, introduced into the blood through a scratch or otherwise, is said to be fatal to man.

Dr. Percy Wilde was the first to suggest the use of ouabaïo in asthma and whooping-cough, but I am not aware whether he has actually employed it in these diseases. So far as I know, the following observations are the first on record of the use of ouabain in practical therapeutics. In this instance its use has been limited to cases of whooping-cough.

Treatment was begun in the first case on October 31st, 1889, and very small doses were employed at the outset; $\frac{1}{2000}$ grain (or half the lethal dose for a frog) was considered sufficient to start with, but this was quickly found to have little or no effect in controlling the disease. Accordingly the strength of the dose was increased from time to time, until it was found that the standard dose for, say a child aged 5 years, was $\frac{1}{1000}$ grain in solution every three hours. Under this dose, if the case was one of moderate severity, the number of coughs and whoops usually rapidly diminished, but in two cases where the children were much prostrated by the violence and frequency of the cough, even this dose was found to be too small, and to them first $\frac{1}{500}$ grain, and latterly $\frac{1}{250}$ grain was given every three hours. This is equal to about $\frac{1}{10}$ grain daily, and is nearly double the strength of the dose advocated by Professor Gley, who, in a recent communication, estimates the maximum daily dose for an adult as 1 milligramme ($\frac{1}{100}$ grain).

Forty-nine cases of whooping-cough have been treated with ouabain. Of these, 25 have been dismissed well, 4 died, and the remainder are still under observation. Of the 4 fatal cases, 1 died from diphtheria, 1 from tubercular meningitis, 1 from acute capillary bronchitis, and the fourth from gradual and progressive emaciation. None of the fatal cases were under treatment with ouabain for a longer period than 10 days—one of them only for 4—and in all of them ouabain had been stopped at least a week before death took place. In none of the fatal cases were there any symptoms which might have been interpreted as indicative of ouabain poisoning.

Throughout the treatment of these 49 cases, careful record has been kept of the temperature, pulse, respiration, urine, skin, etc., and the effect of the drug on the number and character of the coughs and whoops of each patient in each 24 hours has been

closely watched. Except in one case (a remarkably severe one) treatment was not begun until the patient had been eight days in hospital; this was to enable comparison to be made of the periods before, during, and after treatment. No patient was dismissed until at least a fortnight after the last cough had been heard. It is on the observations mentioned that the following general conclusions are based.

1. Ouabain is of marked benefit during all stages of whooping-cough, and, if carefully used, produces gratifying results. In the first stage, it cuts short the attack; in the second, it reduces the violence and frequency of the cough, and diminishes the number of whoops; and in the third, it hastens convalescence in a remarkable manner. The following cases emphasise this.

CASE I.—C. M., aged 7 years, fifteenth day of illness. On admission (December 2nd) he had 16 coughs with 20 whoops in the first 24 hours. From December 2nd till 9th average daily coughs 14, whoops 11; $\frac{1}{1000}$ grain ouabain was given every 4 hours, beginning on December 9th. The whoops ceased on December 15th, and the coughs on the 23rd. The ouabain was kept up, however, till January 5th; total amount given $\frac{1}{2}$ grain. Patient was dismissed well on January 8th.

CASE II.—M. A. E., aged 7 years, fifty-eighth day of illness. On admission (December 16th) she had 17 coughs with 122 whoops in the first 24 hours; there was also profuse vomiting and bleeding. From December 16th till 25th average daily coughs 16, whoops 74; $\frac{1}{1000}$ grain ouabain was given every four hours, beginning on December 25th. On the 28th it is noted that "the duration of each cough is less, and the violence of each paroxysm undoubtedly diminished." On December 31st there were 8 coughs with 17 whoops, and the bleeding had ceased. On January 5th there were 2 coughs with 4 whoops, and the patient no longer vomited. On January 10th the last whoop was heard, but an occasional cough remained till January 26th, when it also ceased. The ouabain was continued till January 31st, and the patient was dismissed well on February 14th. The total amount of ouabain given was $\frac{3}{10}$ grain nearly.

CASE III.—W. I., aged 7 years, forty-third day of illness. On admission (October 22nd) he had 15 coughs with 34 whoops in the first 24 hours. From October 22nd till 31st average daily coughs 14, whoops 37; $\frac{1}{1000}$ grain ouabain was given every 3 hours, beginning on October 31st. There was a total cessation of whoops on November 6th, and of coughs on November 13th. The ouabain was stopped on November 16th; total amount given, $\frac{1}{10}$ grain nearly. Patient was dismissed well on November 30th.

2. Ouabain is a drug which does not appear to be cumulative; its administration can be stopped suddenly without any ill effect beyond an exacerbation of the whooping-cough; it can be as suddenly resumed.

Date.	Ouabain.	Fits of Coughing.	Whoops.	Day of Illness.
October 16th ...	—	29	38	24th
" 20th ...	—	20	42	28th
" 25th ...	—	23	42	33rd
" 29th ...	—	20	44	37th
" 30th ...	$\frac{1}{2000}$ grain every 4 hours	—	—	38th
November 3rd	—	18	40	42nd
" 4th	Stopped	—	—	43rd
" 10th	—	25	156	49th
" 11th	—	29	144	50th
" 12th	$\frac{1}{1000}$ grain every 4 hours	27	88	51st
" 16th	$\frac{1}{1000}$ grain every 4 hours	19	38	55th
" 24th	—	13	28	63rd
December 7th	—	3	2	76th

The foregoing table shows the action of the drug in the case of a child 1 year old. Similar results have been observed in similar circumstances in other three cases.

3. Ouabain should be given, at first at any rate, in doses not larger than $\frac{1}{1000}$ grain every three hours ($\frac{1}{10}$ grain daily).

4. For children under 1 year of age the dose should not exceed $\frac{1}{2000}$ grain every three hours.

5. In children of from 6 to 12 years of age, if the cough be very violent, and the whoops are numerous, $\frac{1}{1000}$ grain may be given in each dose, but the action of the drug must be carefully watched.

6. Ouabain may be given alone, dissolved in water, or in combination with potas. bromid., or chloral hydrate. The simplest way is to dissolve one grain of ouabain in distilled water, so that each