REPORT ON PHYSIOLOGY

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Effect of Apnœa on Convulsions.

Filehne *(Reichert and Du Bois Reymond's Archiv,* 1873, p. 361) reports experiments made under Munk's directions to determine the effect of forced artificial respiration on the normal respiratory movements and on the convulsions produced by strychnia. The author confirms the conclusions of Rosenthal, and rejects those of Brown-Séquard *(Archives de Physiologie,* iv. p. 204). For a better comprehension of the subject, a brief account of the experiments and conclusions of the latter observer may be given. Having found that in guinea pigs, rendered artificially epileptic, the attacks could be cut short by directing a stream of carbonic acid forcibly against the mucous membrane of the pharynx, Brown-Séquard was led to suppose that the arrest of the movements of respiration (apnœa) and of strychnia convulsions, which is effected by forced artificial respiration, is due, not to a superoxygenation of the blood, as Rosenthal supposed, but to an inhibitory action of the vagus, and perhaps other nerves, on the nervous centres of the medulla and cord. Three series of experiments lent force to this hypothesis. In the first place, it was found, that after section of the cervical cord or the vagus nerves, forced artificial respiration produced neither apnœa nor arrest of strychnia convulsions. Secondly, injection of carbonic acid from below upwards through the larynx (the animal breathing through a tracheal canula) caused immediate arrest of respiration. Thirdly, injection of carbonic acid into the lungs caused immediate cessation of the convulsions due to loss of blood.

These experiments of Brown-Séquard, Filehne repeats and criticizes. He finds, in the first place, that neither the section of the cervical cord nor that of the vagus nerves prevents the production of apnœa by artificial respiration. It does not occur so readily as under normal conditions, owing, as Filehne supposes, to disturbances of the circulation, caused by these nervous lesions. He finds, too, that strychnia convulsions are stopped by artificial respiration, as described by Rosenthal, and that the fatal effects of the poison can thus be warded off. In this respect, his observations are at variance with those of Rossbach *(Centralblatt für die medicinischen Wissenschaften,* 1873, p. 369), who denies that artificial respiration has any effect upon the intensity or the duration of the strychnia convulsions. This discrepancy Filehne explains by supposing that Rossbach did not use animals sufficiently alike in all respects for making comparative experiments.

In regard to the effect of section of the vagi on this saving influence of forced respiration in strychnia poisoning, Filehne finds that a dose of strychnia, the effects of which can be warded off by forced respiration, becomes fatal on section of the vagi, but he also finds that an animal poisoned with strychnia and with vagi cut may be saved from death by forced respiration, while an animal similarly treated, but left to breathe naturally, dies in violent tetanus. He therefore concludes that the effect of section of the vagi in rendering fatal a non-fatal dose

of strychnia is due to a disturbance of the circulation which prevents the thorough oxygenation of the blood in spite of the vigorous artificial respiration. The fact that the first appearance of tetanus in an animal thus treated coincides with a sensible diminution in the force of the heart's contractions, is an argument in favor of this view.

Filehne has also studied the effect of a stream of carbonic acid on the nasal and pharyngeal mucous membrane, and finds that when the stream is so directed that the gas comes in contact with the mucous membrane of the nostrils an arrest of the respiratory movements at once takes place, whereas no such effect is produced when the irritation is applied to the trachea, larynx or fauces. This is a reflex, inhibitory phenomenon, the nature of which has been carefully studied by Kratschmer (*Wiener Sitzungs berichte*, Band 62, abth. ii. June 17, 1870), who has recognized the trigeminal nerve as the channel through which the inhibitory influence is conveyed. Filehne and Brown-Séquard agree, therefore, in regarding the arrest of respiration by a stream of carbonic acid directed into the air passages as an inhibitory phenomenon, though the latter observer does not, like the former, limit the surface, the irritation of which produces this effect, to the nasal mucous membrane.

Brown-Séquard's error is, according to Filehne, in confounding the stoppage of respiration thus produced with true apnœa, which depends upon superoxygenation of the blood. Filehne finally makes experiments to determine whether the irritation by carbonic acid can produce not only stoppage of respiration, but also, as Brown-Séquard maintains, arrest of strychnia convulsions, and of artificially produced epilepsy.

By the most carefully conducted experiments, he fails to convince himself that the stream of carbonic acid has any effect in shortening the convulsions either of strychnia or epilepsy. How such discordant results are to be reconciled is not easy to see, but Filehne suggests that, owing to the short and irregular duration (¼′–1′) of the artificial epileptic attacks, one can readily deceive one's self as to the effect of applications made to arrest them.

In this connection must also be mentioned the experiments of Ananoff (*Centralblatt für die medicinischen Wissenschaften*, 6 June, 1874) on the effect of oxygen on increased reflex irritability.

This observer gave a fatal dose of strychnia to two rabbits, and allowed one of them to breathe oxygen, while the other breathed atmospheric air. The latter died in convulsions seven minutes after the administration of the poison, while the former had no convulsions whatever as long as the respiration of oxygen was kept up (twenty-eight minutes), and finally died with only slight spasms ten minutes after the oxygen had been removed. Inasmuch as the oxygen was conducted from the gasometer to the lungs of the animal under a certain pressure, it was necessary to determine whether atmospheric air, breathed under the same pressure, would not produce the same effect. For this purpose, two rabbits were poisoned with strychnia, as before, and one of them made to breathe air coming from the gasometer under pressure, while the other breathed under natural conditions. In the former, tetanic spasms were produced by external irritation seven minutes, and death followed twenty minutes after the administration of the poison, while the latter died at the end of six minutes.

A third experiment was made to determine the difference between

the effect of oxygen and that of an increased amount of atmospheric air. Of two rabbits, both poisoned with strychnia, it was found that the one which breathed oxygen remained free from spasms as long as the oxygen inhalation was kept up, while the one which breathed atmospheric air under pressure had convulsions in seven, and died in twenty, minutes. From this, it seems evident that it is really the presence of oxygen in the blood which prevents the occurrence of strychnia convulsions, and from Rosenthal's experiments it is clear that the amount of oxygen necessary to produce this effect can be forced into the blood by artificial respiration without having recourse to the inhalation of pure oxygen, though in the experiments of Ananoff the effect of breathing condensed air was only to retard and not to prevent the convulsive action of the poison.

MUSCLES.

Ranvier (*Archives de Physiologie*, vi. p. 5) calls attention to the difference in appearance and physiological properties presented by the striped muscles of the same animal. He finds, for instance, that in the leg of the rabbit the semi-tendinosus, the adductor brevis, the quadratus femoris and the soleus have a redder color than the rectus, the vasti, the adductor magnus, the biceps, the gemelli, &c., which, in contrast to the others, are denominated "pale muscles." This difference in color is independent of the amount of blood which the muscles contain, for it persists after the vessels of the limb have been washed out with artificial serum. Corresponding to this difference in appearance is a difference in the nature of the contraction. The red muscle contracts much less promptly than the pale muscle under the influence of an electrical stimulus, and relaxes much more slowly when the stimulus is removed. The period of latent irritation and the duration of the single muscular impulse or shock* is from four to six times greater in the red than in the pale muscles, while the rapidity of stimulation which is sufficient to produce complete tetanus is correspondingly less. These differences are equally manifest, whether the irritation is applied to the nerve or directly to the muscle.

Histological differences are also noticed in the two sorts of muscles. In the pale muscles, the transverse striation is much more distinct than the longitudinal, while in the red muscles the longitudinal striation is very well marked, and the transverse striæ are not straight, as in the pale muscles, but formed of broken lines. Nuclei are much more abundant in the red than in the pale fibres. Muscles presenting these same differences are also found in various species of fish.

Ranvier has also recently reported to the Société de Biologie (*Révue Scientifique*, 6 June, 1874) a very ingenious method of studying the transverse striæ of muscles. The method consists in using a histological preparation of a striped muscle for the production of a diffraction spectrum, the striæ of the muscle producing the same effect upon the light as the fine lines ruled on glass, which are usually employed for this purpose. The spectrum thus produced is found to undergo no change when the muscle contracts, proving that the transverse striæ of muscles do not disappear in contraction, as has been sometimes maintained.

* It would, perhaps, be well to adopt the word "jerk," as the equivalent of the French "secousse" or the German "zuckung," to express the contraction of a muscle in consequence of a single instantaneous irritation.

Glycogenesis.

Since the publication of the report on the glycogenic function of the liver, in January, 1873, considerable progress has been made in our knowledge of this function. The results of recent investigations have been admirably presented by Dr. T. Lander Brunton, in three lectures on the pathology and treatment of diabetes mellitus, published in the *British Medical Journal* for January and February, 1874. To these the reader is referred for details which would be out of place in this report.

The so-called glycogenic function of the liver really consists of two separate and distinct processes: first, the formation of glycogen from the materials supplied by the food and its accumulation in the cells of the liver; and, secondly, the change of this glycogen into sugar and its return to the circulation. The liver thus acts as a storehouse, in which organic substances can be held in reserve when presented in quantities greater than are needed for the immediate use of the organism, and from which they can be given out in a form adapted for rapid consumption whenever they may be needed. In this respect, the liver is analogous to the roots and seeds of plants, which accumulate starch and cane sugar during one season's growth, and at some subsequent period change it to glucose to provide for the further growth of the plant or for germination. This and other interesting analogies between plants and animals have been pointed out by Bernard in his lectures on "vital phenomena common to plants and animals." (*Revue Scientifique*, July–December, 1872.)

It must not be supposed, however, that the liver is the only organ which acts in this way to store up organic substances for future use. The muscles have this same power, and it has been shown by Weiss (*Wiener Sitzungsberichte*, lxiv. p. 284) that they retain their glycogen more tenaciously than the liver, for a considerable amount of glycogen has been found in the muscles of starved animals after it has entirely disappeared from the liver, and muscles are found to retain their irritability as long as glycogen remains present in them. In the embryo, nearly all the tissues are found to contain glycogen. In fact, wherever future growth or work is to be provided for, there glycogen seems to be accumulated.

The first question which presents itself in the study of glycogenesis is: What is the origin of glycogen? The experiments of Dock, already reported,* have shown that the ingestion of glucose increases the amount of glycogen in the liver, and point to the direct transformation, by a process of dehydration, of the former substance into the latter. This view derives confirmation from the experiments of Schöpffer (*Archiv für exp. Pathologie*, i. p. 73), who, following the lead of Bernard, injected a solution of glucose into the crural vein of a rabbit, and found that glycosuria resulted, while a similar injection into a radicle of the portal vein had no such effect, provided that it was not made too rapidly. It seems, therefore, that the liver has the power of removing from the blood, and storing up in the form of glycogen, the glucose brought to it from the intestine by the portal vein. This power is, however, not unlimited; for, if the sugar be brought too rapidly into the portal system, either by absorption (Bernard *Revue*

* This Journal, January 23, 1873.

Scientifique, ii. 1066) or by direct injection, a portion of it will pass unchanged through the liver, reach the general circulation and be excreted by the kidneys. A similar effect may be produced by a ligature on the portal vein (Bernard, *Revue Scientifique*, ii. 1108). Here the sugar absorbed from the intestine reaches the general circulation by collateral channels, causing glycæmia and glycosuria. In this connection, it is interesting to note a case of diabetes reported by Andral, in which the autopsy showed obliteration of the portal vein. It should be mentioned here that the blood of the portal vein seems to contain sugar in an appreciable amount only while digestion is going on.

Many observations seem to show that the glycogen of the liver may also be formed from albuminoid substances. Bernard has shown that the liver of a dog fed upon lean meat contains a much greater quantity of glycogen than that of a fasting animal. Starving dogs, fed on gelatine and fibrin, have also been found to have an increased amount of glycogen in the liver. In the report of January, 1873, reasons were given for supposing that a certain amount of albuminoid material is absorbed unchanged from the intestine and is used for the formation of the tissues, while the peptones, after absorption, are not reconverted into albumen, &c., but, by successive decompositions, reach the form of urea and are thus excreted. A natural extension of this hypothesis is, that the liver is the organ where the decomposition of peptones chiefly takes place, and that glycogen is the form in which the non-nitrogenous products of this decomposition are stored up. The occurrence of nitrogenous substances in the bile may be regarded as an argument in favor of this view. On the other hand, it has been found by Weiss (*Centralblatt für die medicinischen Wissenschaften*, 1873, p. 552) that hens, kept on a diet of fresh meat and fibrin, lose nearly the whole of the glycogen from their livers. How far this is to be regarded as indicating a fundamental difference between birds and mammalia is a question to be settled by future investigations.

There seems to be a pretty general agreement among those who have occupied themselves with the question of glycogenesis, that fatty substances in the food do not give rise to glycogen in the liver. It has, however, been shown by Luchsinger (*Pflüger's Archiv*, viii. 289) that glycerine, when taken into the stomach, causes an increase of glycogen in the liver; owing, probably, to a direct transformation of glycerine into glycogen, and not, as Weiss (*loc. cit.*) supposes, to the glycerine being used up in the place of the glycogen, thus allowing the latter to accumulate. It seems, therefore, probable (though not yet demonstrated) that the ingestion of fats may produce a similar effect, for Kühne (*Physiologische Chemie*, 1868, p. 125) has shown that the pancreatic juice has the power of decomposing neutral fats into fat acids and glycerine.

Whatever may be the particular articles of food which give rise to the formation of glycogen in the liver, there is no doubt that it accumulates in well-fed and disappears in starving animals. A change into glucose is, moreover, a necessary preliminary to its removal from the liver.

The next question, therefore, is: how is this change into glucose effected? That it is a process of fermentation is universally admitted. That the ferment which produces the change is brought to the liver by the blood seems pretty well established, for the observations of

v. Wittisch (*Pflüger's Archiv*, vii. 28) and others, that a change of glycogen into sugar takes place after the vessels of the liver have been washed entirely free from blood, cannot be regarded as proving that the ferment is formed in the hepatic cells, since, as pointed out by Plosz and Tiegel (*Pflüger's Archiv*, vii. 391), the process of washing out the liver with pure water, as practised by v. Wittisch, is well adapted to dissolve out the ferment from the blood globules, which are supposed to contain it, and fix it in the coagulating hepatic parenchyma.

Since, therefore, the ferment in question is contained chiefly, if not wholly, in the circulating blood, it is evident that anything which causes an increased flow of blood through the liver will, by bringing a larger amount of the ferment into contact with the glycogen, produce an increased formation of glucose. If glucose be thus formed in excess of the needs of the system, so that it accumulates in the blood to an amount greater than one-third of one per cent. (Bernard), it will be excreted by the kidneys, and glycosuria will result. Now, an increased flow of blood through the liver may be caused in various ways. In the first place, the stoppage of any of the larger arteries will, by raising the blood tension, force a larger supply of blood through the liver, the calibre of the hepatic vessels being supposed to remain unaltered. This is probably the explanation of the diabetes observed by Schiff as the result of ligaturing large vessels. A rise of blood tension, also, is probably the cause of the diabetes which has been observed in the convulsions of asphyxia (Pavy, *On Diabetes*, pp. 62, 68 and 145) and epilepsy (Trousseau, *Clinique Médicale*, 3d ed., ii. p. 736).

A dilatation of the hepatic vessels, the blood tension remaining the same, will also cause an increased flow of blood through the liver. This dilatation may be the result either of direct or of reflex paralysis of the vaso-motor nerves of the liver. A direct paralysis of these nerves is the probable explanation of the diabetes caused by the section of the anterior columns of the cervical cord (Schiff, *Zuckerbildung*, p. 108), or by extirpation of the last cervical and first dorsal sympathetic ganglion (Cyon and Aladoff, quoted by Brunton, *British Medical Journal*, 1874, p. 39). The experiments of Cyon have rendered it probable that these lesions affect chiefly the size of the hepatic artery, causing little or no change in the calibre of the portal vein.

A reflex paralysis or inhibition of these vaso-motor nerves may be produced by irritation of centripetal fibres in the vagus nerve, and glycosuria may be thus produced (Bernard, *Physiologie Experimentale*, i. pp. 334–339). The well-known effect of a puncture of the floor of the fourth ventricle in producing glycosuria is probably to be referred, in part at any rate, to an irritation of the vagus nerves at their origin, while the glycosuria sometimes noticed as the result of ether and chloroform inhalation (Schiff, *Zuckerbildung*, 124) seems to be due to an irritation of the same nerves at their terminations in the lungs. It would seem, however, from recent observations of Seelig (*Centralblatt für die medicinischen Wissenschaften*, 1873, p. 934) that the "sugar puncture" not only causes an increased change of glycogen into sugar in the liver, but also prevents the sugar which is brought to the liver by the portal vein from being stored up as glycogen in that organ. Seelig found that a starving animal which had received the "sugar puncture" showed little or no sugar in the urine,

but that an injection of glucose into a mesenteric vein caused immediate glycosuria, while a similar injection into a starving animal which had received no "sugar puncture" had no such effect. Similar results were obtained by injection of glucose into the jugular vein, proving, according to Seelig, that "the diabetic animal is characterized by an inability to use sugar for the nourishment of its body." These results are hardly to be explained on the supposition that the "sugar puncture" causes merely a dilatation of the hepatic vessels, allowing more of the ferment contained in the blood to come in contact with the glycogen of the liver. Further experiments are needed, before any satisfactory hypothesis can be advanced.

The third question which presents itself in the study of glycogenesis is: What is the destination of the glucose which is formed in the liver in the manner above described? That the healthy organism is able to consume all the sugar formed within itself is evident from the fact that normal urine contains no appreciable amount of sugar. It would even seem from the experiments of Tieffenbach (*Centralblatt für die medicinischen Wissenschaften*, 1869, p. 179) that still larger amounts may be consumed, for it was found that *small quantities* of glycogen or glucose could be injected into the veins or under the skin without causing glycosuria. In what particular part of the body sugar is consumed is a question not easy to settle, for it has been shown that sugar disappears very rapidly from the blood when withdrawn from the body. Hence, the importance of the rule laid down by Bernard (*Revue Scientifique*, iii. 43), when testing the blood for sugar only to use warm blood fresh from the vessels of the animal. It is not improbable that a similar rapid disappearance of sugar takes place in the circulating blood, irrespective of the organs through which it circulates. There is, however, reason to suppose that a very considerable sugar consumption takes place in the muscles, for it has been shown by Genersich (*Ludwig's Arbeiten*, 1870, p. 75) that defibrinated blood loses sugar on being conducted through a dog's hind legs, freshly separated from the body, and still retaining their muscular irritability. This disappearance of sugar is, moreover, quite in accordance with what is known of the effect of muscular activity in increasing the exhalation of carbonic acid. It cannot be supposed, however, that glucose is directly oxidized to carbonic acid, for it has been shown (Bernard, *Physiologie Experimentale*, i. 241) that blood shaken with oxygen does not lose its sugar faster than with other gases. Moreover, it has been found that as sugar disappears from the blood lactic acid takes its place, and muscles when kept in prolonged activity are found to have an acid reaction, due to the formation of lactic acid within them. There is, therefore, no reason to doubt that a change into lactic acid by a process of fermentation is the first step in the disappearance of glucose from the organism. This view is also in accordance with the observations of Scheremetjewski (*Ludwig's Arbeiten*, 1868, p. 114), who found that the injection of alkaline lactates into the blood caused an increased absorption of oxygen and exhalation of carbonic acid, while an injection of glucose had no such effect.

The experiments of Schultzen on phosphorus poisoning (*Zeitschrift für Biologie*, viii. 124, and *Berliner Klinische Wochenschrift*, 1872, p. 417) throw light upon this subject. The action of phosphorus is, according to Schultzen, to arrest the processes of oxidation in the organ-

ism, while those of fermentation go on unchecked. He finds that in animals poisoned by phosphorus "urea disappears from the urine, and is replaced by leucine and tyrosine, which, in the healthy organism, are converted into urea. No sugar appears in the urine, but a kind of lactic acid is found in quantities exactly proportional to the amount of sugar afforded to the animals by their food. This kind of lactic acid agrees exactly in its properties with the aldehyde of glycerine, and Schultzen considers the two bodies to be identical."* The production of this substance from glucose by a process of fermentation seems, therefore, to be a necessary preliminary to oxidation, and if for any reason this preparatory fermentation does not take place, the glucose, not being oxidizable as such, is excreted by the kidneys, and glycosuria results. This seems to be the case in some forms of diabetes, and in the experiments of Scheremetjewski, above alluded to.

To recapitulate briefly. The liver has two functions:—1st, that of forming and storing up glycogen; and, 2d, that of forming sugar again from glycogen. The muscles probably possess both of these functions, and also a third function, viz., that of changing both the sugar they form and the greatest part of that which they receive from the blood into lactic acid, which undergoes combustion.

Glycosuria may result,

1st, from failure of the liver to convert into glycogen the sugar obtained from the food, either because it is brought in too large quantities to the liver, or because the liver has not the power to effect the change in question. This may be called alimentary glycosuria, and may be prevented by avoiding saccharine articles of food.

2d, from an increased transformation of glycogen into sugar, due to accelerated circulation through the liver, or to a larger proportion of ferment in the organ or the blood. (The possible participation of the muscles in the production of both these sorts of glycosuria must be borne in mind.)

3d, from a diminished consumption of sugar in the organism, "due either (a) to insufficiency of the ferment, which should convert the sugar into lactic acid, (b) to an altered quality of the sugar which enables it to resist the action of the ferment, or (c) to diminished circulation through the muscles preventing the sugar from coming sufficiently into contact with the ferment."†

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* Brunton's third lecture, loc. cit.

† Brunton, loc. cit.

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