the substance of the liver and in the blood of the hepatic veins as due to post-mortem action, and his observations seemed to be directly opposed to those of Bernard. The views of these two observers and their followers seemed to be harmonized by a series of experiments made in 1868. If the abdomen of a dog, perfectly quiet and not under the influence of an anæsthetic, be opened, and a portion of the liver be excised, rinsed in cold water and rapidly cut up into boiling water, the extract will show no reaction with Fehling's test for sugar. In one experiment, in which twenty-eight seconds elapsed between the time of opening the abdomen and the action of the boiling water, the reaction with Fehling's test was doubtful. In an experiment in which the time was only ten seconds, there was no trace of sugar in the extract from the liver (Flint). Dalton, however, in 1871, found small quantities of sugar in extracts of portions of liver taken from an animal in an average time of $6\frac{1}{4}$ seconds; but it is possible that the sugar may have been in blood retained in the liver. All observers, however, are now agreed that sugar is formed in the liver very rapidly after death.

If the view be correct, that the glycogen of the liver is being constantly transformed into sugar during life, and that this sugar is carried away in the blood-current, as fast as it is formed, sugar would not necessarily be contained in the liver under normal conditions; and there is no actual antagonism between the results obtained by Bernard and the fact that sugar itself is not a normal constituent of the liver, as is asserted by Pavy, McDonnell, Meissner, Ritter and others.

If the liver be washed by a stream of water passed through its vessels until it is free from sugar, and if it be kept at the temperature of the body for a few hours, sugar will appear in abundance (Bernard, 1855). This is due to a conversion of the glycogen of the liver into sugar by a ferment, which has been extracted and isolated by Bernard and others by a process analogous to that by which similar ferments have been extracted from the saliva and the pancreatic juice. This ferment probably exists originally in the liver and does not appear first in the blood.

The question of the transformation of glycogen into sugar during life depends upon the comparative quantities of sugar in the blood going to and coming from the liver. Bernard always found sugar in quantity in the blood of the hepatic veins taken immediately after death, and it exists in blood drawn during life by a catheter introduced into the right cavities of the heart; while in the carnivora, under a purely animal diet, no sugar is contained in the blood of the portal system. The normal blood contains, perhaps, a small quantity of sugar—0·5 to 1 part per 1,000—but the proportion is always greater in the blood of the hepatic veins.

The characters of animal sugar do not materially differ from those of glucose, except that it ferments more readily and is destroyed in the system with great facility. This property of the sugar which results from the glycogen formed in the liver is probably of great importance. The sugar which results from digestion is all carried to the liver. Here it is changed into glycogen; and it is probable that without this change into glycogen and its

subsequent transformation into what is called liver-sugar, it is not perfectly adapted to the purposes of nutrition. In many cases of diabetes, a possible explanation of the glycosuria is that the carbohydrates pass unchanged into the vena cava and do not undergo the changes which take place normally in the liver, at the same time being received into the general circulation suddenly and in large quantity, instead of gradually, as when they are changed into glycogen and afterward into liver-sugar. When an excess of sugar finds its way into the blood, it is probable that the liver, under normal conditions, retains it for a time in the form of glycogen.

The sugar which is discharged into the venous system by the hepatic veins is usually lost in the passage of the blood through the lungs. The question of the final destination of sugar will be taken up again in connection with the physiology of nutrition.

Conditions which influence the Quantity of Sugar in the Blood.—It is probable that disturbances of the circulation in the liver are the most important conditions influencing the discharge of sugar by the hepatic veins, and these operate mainly through the nervous system.

The most remarkable experiment upon the influence of the nervous system on the liver is the one in which artificial diabetes is produced by irritation of the floor of the fourth ventricle (Bernard). This operation is not difficult. The instrument used is a delicate stilet, with a flat, cutting extremity, and a small, projecting point about $\frac{1}{25}$ of an inch (1 mm.) long. In performing the operation upon a rabbit, the head of the animal is firmly held in the left hand, and the skull is penetrated in the median line, just behind the superior occipital protuberance. This can easily be done by a few lateral movements of the instrument. Once within the cranium, the instrument is passed obliquely downward and forward, so as to cross an imaginary line drawn between the two auditory canals, until its point reaches the basilar process of the occipital bone. The point then penetrates the medulla oblongata, between the roots of the auditory nerves and the pneumogastrics, and by its projection it serves to protect the nervous centre from more serious injury from the cutting edge. The instrument is then carefully withdrawn and the operation is completed. This experiment is almost painless, and it is not desirable to administer an anæsthetic, as this, in itself, would disturb the glycogenic process. The urine may be drawn before the operation, by pressing the lower part of the abdomen, taking care not to allow the bladder to pass up above the point of pressure, and it will be found turbid, alkaline and without sugar. In one or two hours after the operation, the urine will have become clear and acid, and it will react readily with any of the copper-tests. When this opera-

FIG. 137.—*Instrument for puncturing the floor of the fourth ventricle* (Bernard).

tion is performed without injuring the adjacent organs, the presence of sugar in the urine is temporary, and the next day the secretion will have returned to its normal condition. The production of diabetes in this way, in animals, is important in its relations to certain cases of the disease in the human subject, in which the affection is traumatic and directly attributable to injury near the medulla. Its mechanism is difficult to explain. The irritation is not propagated through the pneumogastric nerves, for the experiment succeeds after both of these nerves have been divided; nevertheless, the pneumogastrics have an important influence upon glycogenesis. If both of these nerves be divided in the neck, in a few hours or days, depending upon the length of time that the animal survives the operation, no sugar is to be found in the liver, and there is reason to believe that the glycogenic action has been arrested. After division of the nerves in the neck, stimulation of their peripheral ends does not affect the production of sugar; but stimulation of the central ends produces an impression which is conveyed to the nervous centre, is reflected to the liver and gives rise to an increased production of sugar.

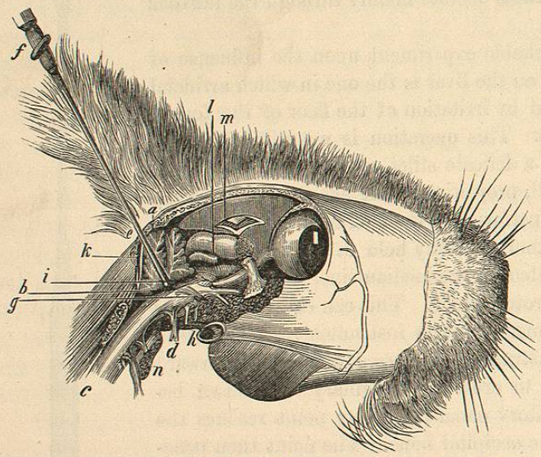

FIG. 138.—*Section of the head of a rabbit, showing the operation of puncturing the floor of the fourth ventricle* (Bernard).

a, cerebellum; *b*, origin of the seventh pair of nerves; *c*, spinal cord; *d*, origin of the pneumogastric; *e*, opening of entrance of the instrument into the cranial cavity; *f*, instrument; *g*, fifth pair of nerves; *h*, auditory canal; *i*, extremity of the instrument upon the spinal cord, after it has penetrated the cerebellum; *k*, occipital venous sinus; *l*, tubercula quadrigemina; *m*, cerebrum; *n*, section of the atlas.

With regard to the influence of the sympathetic nerves upon glycogenic action, there have been few if any experiments which lead to conclusions of any great value.

It has been observed that the inhalation of anæsthetics and irritating vapors produces temporary diabetes; and this has been attributed to an irritation conveyed by the pneumogastrics to the nerve-centre, and reflected, in the form of a stimulus, to the liver. It is for this reason that the administration of anæsthetics should be avoided in all accurate experiments on glycogenic action.

The following summary expresses what is known with regard to the production of glycogen by the liver and its conversion into sugar:

A substance exists in the healthy liver, which is readily convertible into sugar; and inasmuch as this is changed into sugar during life, the sugar being washed away by the blood passing through the liver, it is proper to call it glycogen, or sugar-forming matter.

The liver has a glycogenic action, which consists in the constant formation of sugar out of the glycogen, the sugar being carried away by the blood of the hepatic veins, which always contains sugar in a certain proportion. This production of sugar takes place in the carnivora, as well as in those animals that take sugar and starch as food; and it is to a certain extent independent of the kind of food taken.

During life the liver contains glycogen only and no sugar, because the blood which is constantly passing through this organ washes out the sugar as fast as it is formed; but after death or when the circulation is interfered with, the transformation of glycogen into sugar continues. The sugar is not removed under these conditions, and it can then be detected in the substance of the liver.

The liver serves as a receptacle for the carbohydrates, which, under normal conditions of alimentation and nutrition, are all converted into glycogen. The glycogen is then converted into sugar, which is supplied to the system as the nutritive requirements demand.

In addition to the varied uses of the liver which have been described, it is thought that this organ either arrests or in some way influences the condition of certain foreign and poisonous substances which may be absorbed from the alimentary canal; but a study of this action does not properly belong to physiology.

Ductless Glands.

Certain organs in the body, with a structure resembling, in some regards, the true glands, but without excretory ducts, have long been the subject of physiological speculation; and the most extravagant notions concerning their uses have prevailed in the early history of physiology. The discovery of the action of the liver, which consists in modifications in the composition of the blood passing through its substance, has foreshadowed the probable mode of action of the ductless glands; for as far as the production of glycogen is concerned, the liver belongs to this class. Indeed, the supposition that the ductless glands effect certain changes in the blood is now regarded by physiologists as the most reasonable of the many theories that have been entertained concerning their uses in the economy. Under this idea, these organs have been called blood-glands or vascular glands. Under the head of ductless glands, are classed the spleen, the suprarenal capsules, the thyroid gland, the thymus, and sometimes the pituitary body and the pineal gland.

Physiological Anatomy of the Spleen.

The spleen is situated in the left hypochondriac region, next the cardiac extremity of the stomach. Its color is a dark bluish-red and its consistence is rather soft and friable. It is shaped somewhat like the tongue of a dog, presenting above, a rather thickened extremity, which is in relation with the diaphragm, and below, a pointed extremity, in relation with the transverse colon. Its external surface is convex. Its internal surface is concave, presenting a vertical fissure, the hilum, which gives passage to the vessels and

nerves. It is connected with the stomach by the gastro-splenic omentum and is still farther fixed by a fold of peritoneum passing to the diaphragm. It is about five inches (127 mm.) in length, three to four inches (75 to 100 mm.) in breadth, and a little more than an inch (25·4 mm.) in thickness. Its weight is six to seven ounces (170 to 198 grammes). In the adult it attains its maximum of development, and it diminishes slightly in size and weight in old age. In early life it bears about the same relation to the weight of the body as in the adult.

The external coat of the spleen is the peritoneum, which is very closely adherent to the subjacent fibrous structure. The proper coat is dense and resisting, but in the human subject it is quite thin and somewhat translucent. It is composed of ordinary fibrous tissue mixed with abundant small fibres of elastic tissue and a few non-striated muscular fibres.

At the hilum the fibrous coat penetrates the substance of the spleen in the form of sheaths for the vessels and nerves. The number of the sheaths in the spleen is equal to the number of arteries that penetrate the organ. This membrane is sometimes called the capsule of Malpighi. The fibrous sheaths are closely adherent to the surrounding substance but they are united to the vessels by a loose, fibrous net-work. They follow the vessels in their ramifications to the smallest branches and are lost in the spleen-pulp. Between the sheath and the outer coat, are bands, or trabeculæ, presenting the same structure as the fibrous coat. The presence of elastic fibres in the trabeculæ can be easily demonstrated, and this kind of tissue is very abundant in the herbivora. In the carnivora the muscular tissue is particularly abundant and can be readily demonstrated; but in man this is not so easy, and the fibres are less abundant. These peculiarities in the fibrous structure are important in their relations to certain physiological changes in the size of the spleen. Its contractility may be easily demonstrated in the dog, by the application of a Faradic current to the nerves as they enter at the hilum. This is followed by a prompt and enegetic contraction of the organ. Contractions may be produced, though they are much more feeble, by applying the current directly to the spleen.

The substance of the spleen is soft and friable; and a portion of it, the spleen-pulp, may be easily pressed out with the fingers or even washed away by a stream of water. Aside from the vessels and nerves, it presents for study: 1, an arrangement of fibrous bands, or trabeculæ, by which it is divided into communicating spaces; 2, closed vesicles, called Malpighian bodies, attached to the walls of the blood-vessels; 3, a soft, reddish substance, containing large numbers of cells and free nuclei, called the spleen-pulp.

Fibrous Structure of the Spleen (*Trabeculæ*).—From the internal face of the investing membrane of the spleen and from the fibrous sheath of the vessels (capsule of Malpighi), are bands, or trabeculæ, which, by their interlacement, divide the substance of the organ into irregularly shaped, communicating cavities. These bands are $\frac{1}{25}$ to $\frac{1}{15}$ of an inch (1 to 1·7 mm.) broad, and are composed, like the proper coat, of ordinary fibrous tissue with elastic fibres and probably a few non-striated muscular fibres. They pass off from

the capsule of Malpighi and the fibrous coat at right angles, very soon branch, interlace, and unite with each other, becoming smaller and smaller, until they measure $\frac{1}{250}$ to $\frac{1}{60}$ of an inch (0·1 to 0·42 mm.). This fibrous net-work serves as a support for the softer and more delicate parts.

Malpighian Bodies.—These bodies are sometimes called the splenic corpuscles or glands. They are rounded or slightly ovoid, about $\frac{1}{50}$ of an inch (0·5 mm.) in diameter, and are filled with what are thought to be lymph-corpuscles, and free nuclei. The Malpighian bodies have no investing membrane. With this difference, they resemble in structure the solitary glands of the intestine. Both the cells and the free nuclei of the splenic corpuscles bear a close resemblance to cells and nuclei found in the spleen-pulp. The corpuscles are surrounded by blood-vessels—which send branches into the interior, to form a delicate, capillary plexus—and by what is thought to be a lymphatic space or sinus.

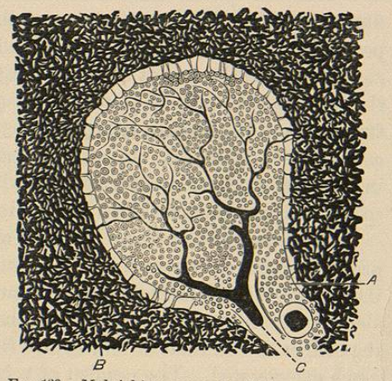

FIG. 139.—*Malpighian corpuscle of the spleen of the cat* (Cadiat).
A, artery around which the corpuscle is placed; B, meshes of the pulp, injected; C, the artery of the corpuscle ramifying in the lymphatic tissue. The clear space around the corpuscle is the lymphatic sinus.

The number of the Malpighian corpuscles in a spleen of ordinary size has been estimated at about ten thousand (Sappey). They are readily made out in the ox and sheep but are frequently not to be discovered in the human subject. The occasional absence of these bodies constitutes another point of resemblance to the solitary glands of the small intestine.

The Malpighian bodies are attached to arteries measuring $\frac{1}{80}$ to $\frac{1}{60}$ of an inch (0·32 to 0·42 mm.) or less in diameter (Sappey). They are often found in the notch formed by the branching of an artery, but they usually lie by the sides of the vessel.

Spleen-pulp.—The spleen-pulp is a dark, reddish, semi-fluid substance, its color varying in intensity in different specimens. It is so soft that it may be washed by a stream of water from a thin section, and it readily decomposes, becoming then nearly fluid. It is contained in the cavities bounded by the fibrous trabeculæ, and it contains itself microscopic bands of fibres arranged in the same way. It surrounds the Malpighian bodies and contains the terminal branches of the blood-vessels, nerves and lymphatics. Upon microscopical examination, it presents free nuclei and cells like those described in the Malpighian bodies; but the nuclei are here relatively much more abundant. In addition are found, red blood-corpuscles, some natural in form and size and others more or less altered, with pigmentary granules, both free and enclosed in cells.

Blood-vessels, Nerves and Lymphatics of the Spleen.—The quantity of blood which the spleen receives is very large in proportion to the size of the organ.

The splenic artery is the largest branch of the cœliac axis. It is a vessel of considerable length and is remarkable for its tortuous course. In an observation by Sappey, in a man between forty and fifty years of age, the vessel measured about five inches (12 centimetres), without taking account of its deflections; and a thread placed on the vessel so as to follow exactly all its windings measured a little more than eight inches (21 centimetres). The large caliber of this vessel and its tortuous course are important points in connection with the great variations in the size of the spleen under various conditions in health and disease. The artery gives off several branches to the adjacent viscera in its course, and as it passes to the hilum, it divides into three or four branches, which again divide so as to form six to ten vessels. These penetrate the substance of the spleen, with the veins, nerves and lymphatics, enveloped in fibrous sheaths. In the substance of the spleen the arteries branch rather peculiarly, giving off many small ramifications in their course, generally at right angles to the parent trunk. These are accompanied by the veins until they are reduced to $\frac{1}{80}$ or $\frac{1}{60}$ of an inch (0·32 or 0·42 mm.) in diameter. The two classes of vessels then separate, and the arteries have attached to them the corpuscles of Malpighi. It is also a noticeable fact that the arteries passing in at the hilum have no inosculations with each other in the substance of the spleen, so that the organ is divided up into six to ten vascular compartments.

The veins join the small branches of the arteries in the spleen-pulp and pass out of the spleen in the same sheath. They anastomose quite freely in their larger as well as their smaller branches. Their caliber is estimated as about twice that of the arteries (Sappey). The estimates which have put the caliber of the veins at four or five times that of the arteries are probably much exaggerated. The number of veins emerging from the spleen is equal to the number of arteries of supply.

By most anatomists two sets of lymphatic vessels have been recognized, the superficial and the deep. The superficial lymphatics are in the investing membrane of the spleen and probably are connected with the deep lymphatics. The origin of the deep vessels is somewhat obscure. Lymphatic spaces or sinuses surround the Malpighian bodies, and there is probably a perivascular canal-system, the exact origin of which is unknown. At the hilum the deep lymphatics are joined by vessels from the surface. The vessels, numbering five or six, then pass into small lymphatic glands and empty into the thoracic duct opposite the eleventh or twelfth dorsal vertebra. No lymphatic vessels have been observed going to the spleen.

The nerves of the spleen are derived from the solar plexus. They follow the vessels in their distribution and are enclosed with them in the capsule of Malpighi. They are distributed ultimately in the spleen-pulp, but nothing definite is known of their mode of termination. When these nerves are stimulated, the non-striated muscles in the substance of the spleen are thrown into contraction.

Some Points in the Chemical Constitution of the Spleen.—Very little has been learned with regard to the probable uses of the spleen from analyses of its substance; and it would therefore be out of place to discuss its chemical

constitution very fully. Cholesterine has been found to exist in the spleen constantly and in considerable quantity, and the same may be said of uric acid. In addition, chemists have extracted from the substance of the spleen, hypoxanthine, leucine, tyrosine, a peculiar crystallizable substance called, by Scherer, lienine, crystals of hæmatoidine, lactic acid, acetic acid, butyric acid, inosite, amyloid matter and some indefinite fatty matters.

Variations in the Volume of the Spleen.—One of the theories with regard to the uses of the spleen, which merits some consideration, is that it serves as a diverticulum for the blood when there is a tendency to congestion of the other abdominal viscera.

It has been shown that the spleen is greatly enlarged in dogs four or five hours after feeding, that its enlargement is at its maximum at about the fifth hour, and that it gradually diminishes to its original size during the succeeding twelve hours; but it is not apparent how far these changes are important or essential to normal digestion and absorption. Experiments have shown that animals may live, digest, and absorb alimentary matters after the spleen has been removed, and this has been observed even in the human subject. In view of these facts, it can not be assumed that the office of the spleen, as a diverticulum for the blood, is essential to the proper action of the other abdominal organs.

Changes in the volume of the spleen may be produced by operating on the nervous system, chiefly through the vaso-motor nerves. Section of the nerves at the hilum increases the size of the spleen by increasing the quantity of blood which it receives; and stimulation of these nerves produces contraction of the spleen. It is stated that stimulation of the medulla oblongata diminishes the size of the spleen, and that the same result can be produced by reflex action, stimulating the central ends of the pneumogastrics or of various sensory nerves, provided that the splanchnic nerves be intact. Starting from the medulla oblongata, the nerve-fibres which influence the size of the spleen pass down the spinal cord to the lower dorsal region, enter the semilunar ganglion by the left splanchnic, and are distributed to the spleen through the splenic plexus.

Extirpation of the Spleen.—There is one experimental fact that has presented itself in opposition to nearly every theory advanced with regard to the uses of the spleen, which is that the organ may be removed from a living animal and yet all the processes of life go on apparently as before. The spleen is certainly not necessary to life, nor, as far as is known, is it essential to any of the important general functions. It has been removed from dogs, cats, and even from the human subject, and its absence is attended with no constant and definite changes in the phenomena of life. If it act as a diverticulum, this is not essential to normal digestion and absorption; and if its office be the destruction or the formation of the blood-corpuscles, the formation of leucocytes, of uric acid, cholesterine or of any excrementitious matter, there are other organs which may perform these acts. Extirpation of the spleen is an old and a very common experiment. In the works of Malpighi, published in 1687, is an account of an experiment on a dog, in which the