interchange of gases between the blood on the one side of the respiratory epithelium and the alveolar air on the other side take place by a mere process of diffusion, or does the functional activity of the epithelial cells exert some controlling or modifying influence? Our answer to this question must be determined by a consideration of what we know of the properties of epithelium elsewhere, and by the possibility of explaining the interchange on a purely physical basis.

There is an increasing tendency to attribute more importance to lining epithelium in the absorption and secretion of liquids and solids. This is seen in the change that has recently taken place in the teaching of the text-books with regard to intestinal absorption and the process of secretion. The fact that epithelium may also play an active part in the secretion of gases has been amply demonstrated by a number of investigators in connection with the secretion of gases in the swim bladder of fishes. Bohr has shown that this process is under nervous control.

With regard to the possibility of explaining the interchange of gases in the mammalian lung on a purely physical basis, it might be explained by the laws of simple diffusion and osmosis if the partial pressures on the two sides of the epithelium were always such as to favor the exchange that takes place. This question has been investigated as follows: First air is drawn off from the alveoli by one of the instruments devised for the purpose, of which *Pflüger's lung catheter* is the best known. Then this air is analyzed and the partial pressure of each gas in the alveoli can be calculated. Next the partial pressures of the gases in arterial and venous blood are estimated by some form of *aërotonometer* or *hæmataërometer*, and a comparison of the results obtained from the alveolar air and the arterial and venous blood in any given case will show whether the partial pressures are favorable to the interchange or not. The principle of the *aërotonometer* is as follows: It is an apparatus in which blood is brought into close relation with two gaseous mixtures, in one of which the CO_2 tension is above, while in the other it is below the anticipated tension of the blood. As blood flows through the apparatus an interchange of gases takes place between it and the gaseous mixtures contained. By analyzing the latter before and after, the tension of gases in the blood can be approximately determined.

Fredericq gives the following as a typical result of such an investigation in a dog:

	External air.		Alveoli.		Arterial blood.		Tissues.
Tension of oxygen..	20.95	>	18	>	14	>	0
	External air.		Alveoli.		Venous blood.		Tissues.
Tension of carbon dioxide...........	.03	<	2.8	<	3.81-5.4	<	5-9

In this case the tensions or partial pressures of the gases are such that oxygen would tend by mere diffusion to pass in from the air to the blood and CO_2 in the reverse direction.

Other workers, however, notably Bohr, and Haldane and Lorraine Smith, employing somewhat different methods, have obtained results which seem to show that oxygen may be taken in and CO_2 excreted even when the partial pressures are such as to oppose the process. If these experiments are reliable, as seems probable, we must look to some active secretory power of the respiratory epithelium for the explanation.

Dr. Wesley Mills has maintained this view for many years, and his text-book, published in 1889, was one of the first to recognize it in the following terms: "The view expressed by some physiologists to the effect that diffusion explains the whole matter so far at least as carbonic anhydride is concerned, and that the epithelial cells of the lung have no share in the respiratory process, does not seem to be in harmony either with the facts of respiration, or with the laws of biology in general."

THE SEAT OF THE OXIDATION WHICH OCCURS IN THE BODY.—At the beginning of the last century physiologists were divided in opinion as to the principal seat of oxidative processes in the body. Some, who followed Black, believed that these processes took place exclusively in the lungs, while others, led by Le Grange, regarded the blood as the seat of these changes. During the past fifty years Pflüger and others have shown that neither of the old views was correct, but that oxidation is continually taking place in all the tissues, and that it varies to a great extent with their functional activity. It has been shown, moreover, that the taking up of oxygen and giving off of CO_2 do not necessarily run parallel, but that the former may be stored up in excess during rest as tissue oxygen, and may remain in some more or less stable combination until a time of functional activity, when a dissolution of the molecule occurs with the setting free of CO_2. Some of the facts on which these views are founded are the following: If the blood of a frog be replaced by saline solution, the animal may live for hours or days, and continue to take up oxygen and excrete CO_2 (Oertman). Bleeding, although diminishing the quantity of blood in the body, has no effect on the amount of gaseous interchange (Pembrey and Gürber). If a muscle be made to contract *in vacuo*, it will give off CO_2, derived from its tissue oxygen, in sufficient quantity to be determined (Hermann). If a solution of fresh blood be supplied to a frog's heart, the oxyhæmoglobin will be reduced more quickly during activity than during rest (Yeo).

"The avidity of the different tissues for oxygen varies greatly, and the differences are doubtless expressions, broadly speaking, of the relative intensities of their respiratory processes" (Reichert).

Quinquaud records the following absorption capacities for 100 gm. of different tissues submitted for three hours to a temperature of 38° C.:

	C.c.		C.c.
Muscle....................	23	Spleen....................	8.0
Heart......................	21	Lungs......................	7.2
Brain......................	12	Adipose tissue............	6.0
Liver......................	10	Bone......................	5.0
Kidney....................	10	Blood......................	0.8

INTERNAL OR TISSUE RESPIRATION is the term applied to the interchange of gases between the blood and the tissues. The partial pressures of the gases in the tissues, lymph, and blood are said to be such as to favor the taking up of oxygen by the tissues, and the giving off of CO_2 in accordance with well-known physical laws, but this fact does not necessarily exclude some participation of the endothelial and tissue cells in the process.

GRAPHIC RECORD OF RESPIRATORY MOVEMENTS.—Innumerable devices have been employed for this purpose. Some, either because they require a cutting operation or

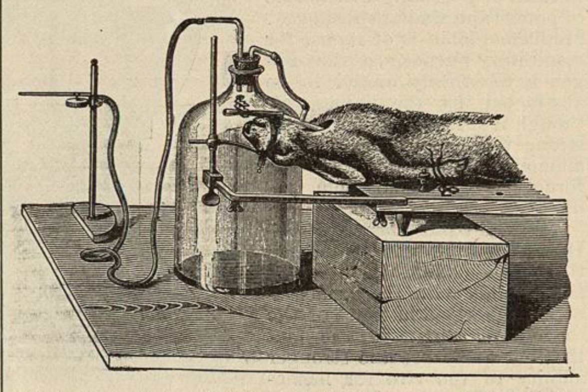

FIG. 4106.—Arrangement of Tracheal Cannula and Marey's Tambour for Recording Changes in Intrapulmonary Pressure. (Langendorff.)

for other reasons, are employed only on animals; and others may be used clinically on man. To the former category belong the *phrenograph*, by which the movements of the diaphragm are recorded by the use of a lever or rubber bag passed up between the liver and dia-

phragm and connected with a recording lever; various forms of sounds and cannulas, which can be passed into the pleural cavity or the œsophagus and connected with a recording tambour to register the variations in intrathoracic pressure; a tracheal cannula or a nose cap from either of which the volume of air breathed can be recorded

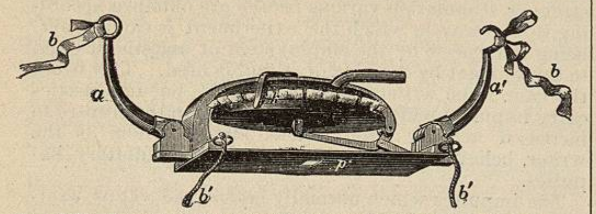

FIG. 4107.—Receiving Tambour of Marey's Pneumograph, New Form. (Langendorff.) *b*, *b*, Belt to go around chest; *b'*, *b'*, strings to suspend the instrument from the neck.

by the *aërophthysmograph* of Gad, or the changes in intrapulmonary pressure can be registered by a Marey's tambour. In either case it is usual to have an air chamber between the animal and the recording apparatus, so that the same air will not be breathed over and over again (see Fig. 4106).

Among the methods which may be employed in man are the *pneumograph* or *stethograph*, in which a belt surrounding the chest is attached to some form of receiving tambour from which a rubber tube leads off to a recording tambour, and indicates the changes in the girth of the thorax (see Fig. 4107). In the *stethometer* of Burdon Sanderson the changes in the antero-posterior diameter of the chest are recorded.

Perhaps the simplest method of all is to connect a recording tambour through a piece of rubber tubing with a small funnel, and to press the latter into the episternal notch. A fair record of the respiration may be obtained in this way.

The curves obtained in these various ways differ in their details, but the tracing shown in Fig. 4108, and obtained with Marey's pneumograph, may be taken as a type.

As the figure shows, inspiration begins somewhat suddenly and advances rapidly, being followed immediately by expiration, which is carried out at first rapidly, but afterward more and more slowly.

NERVOUS MECHANISM OF RESPIRATION.—The muscles of respiration act rhythmically under the influence of nervous impulses, which originate in the medulla oblongata and pass out by the motor nerves. The respiratory centre in the medulla sends out these impulses as the result of a constant stimulus imparted to it by the blood. The explanation of the rhythmic action of the centre under the constant stimulus of the blood is to be sought for in the fundamental properties of protoplasm. The action of the centre is modified by impulses reaching it by afferent nerves, of which some are constantly in operation and others only act occasionally.

The Respiratory Centre.—All the brain above the medulla may be removed without serious interference with the breathing. If the spinal cord be separated from the medulla all respiratory movements of the trunk cease, but some of the facial muscles, still in connection with the medulla through the cranial nerves, continue to exhibit movements of a respiratory character. Injury of the medulla in the lower part of the floor of the fourth ventricle (calamus scriptorius) is sufficient to cause cessation of respiration and death, all the rest of the nervous system being intact. These facts suffice to localize the respiratory centre in the floor of the fourth ventricle, but the exact nerve cells which constitute it cannot be pointed out. From the fact that cessation of respiration has followed injury to different parts in the hands of different investigators, the respiratory centre is probably made up of several separate groups of cells or nerve nuclei and bundles of connecting fibres.

If the medulla be carefully divided in the median line respiration continues; and if the pneumogastric nerve on one side be divided, the movements on that side will become slower than on the other, and we may have the two halves of the diaphragm contracting independently, each with its own rhythm. This shows that the respiratory centre consist of two halves, each more or less complete in itself. Normally, however, they act in harmony, being co-ordinated through commissural fibres, which cross the median line from one side to the other.

From the fact that certain influences affect especially inspiration and others expiration, it seems logical to assume that the respiratory centre is physiologically divided into an inspiratory and an expiratory centre, but we cannot separate these anatomically at present.

Subsidiary Centres.—Stimulation of various parts of the brain gives rise to modification of the respiratory movements. This fact has led to a number of structures, among which are parts of the cerebral cortex, the tuber cinereum, the optic thalamus, the pons Varolii, and the anterior and posterior corpora quadrigemina, being dignified with the name of "*subsidiary respiratory centres.*" As will be shown later, a tonic inhibitory influence seems to be exerted on the respiratory centre by the posterior corpora quadrigemina, but the other structures named are probably mere stations through which afferent impulses from the various sensory nerves may affect the respiratory centre in the medulla. Brown-Séquard, Langendorff, Wertheimer, and others lay great stress on the fact that after separation of the spinal cord from the medulla in young animals a kind of respiration is carried on by the cord alone. It is very different in its character, however, from normal breathing, being "rapid and irregular" (Wertheimer), and in many cases it does not occur at all. One, therefore, feels disposed to look upon these so-called spinal centres for respiration as rather co-ordinating centres for the respiratory muscles, which usually perform their functions under the control of the respiratory centre in the medulla. In some cases they seem to have retained a vestige of their original protoplasmic power of rhythmic activity.

The Influence of the Blood on the Respiratory Centre.—If the amount of oxygen in the blood be diminished or the proportion of carbonic oxide become higher, there follows increased activity of the respiratory centre. The respirations become deeper and often quicker, constituting the condition known as *hyperpnœa*. If the change in the blood be greater the respiratory movements become still more pronounced, additional muscles are called into play, and expiration, which is normally largely passive, becomes an active muscular act like inspiration; this condition is known as *dyspnœa*. Dyspnœa may pass into the condition known as *asphyxia*. The form of asphyxia caused by occlusion of the trachea and deprivation of oxygen is characterized by convulsions, followed by ex-

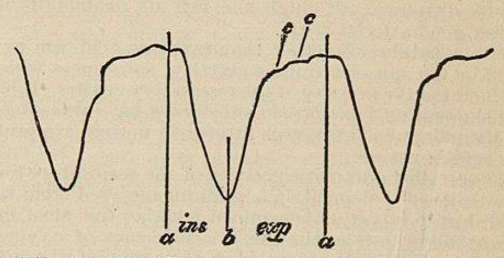

FIG. 4108.—Tracing of Thoracic Respiratory Movements obtained by means of Marey's Pneumograph. (Foster.) A whole respiratory phase is comprised between *a* and *a*; inspiration, during which the lever *descends*, extending from *a* to *b*, and expiration from *b* to *a*. The undulations at *c* are caused by the heart's beat.

haustion and death. In asphyxia due to breathing an atmosphere in which carbonic acid gas is in excess, but where oxygen is not greatly deficient, the animal passes from dyspnœa into a state of stupor, and dies without passing through the stage of convulsions. The condition of the blood affects the centre directly, and not through the afferent nerves, as is shown by the so-called "cross circulation" experiment. In this experiment the neck vessels of two dogs are joined in such a way that the head of each is supplied from the carotid arteries of the

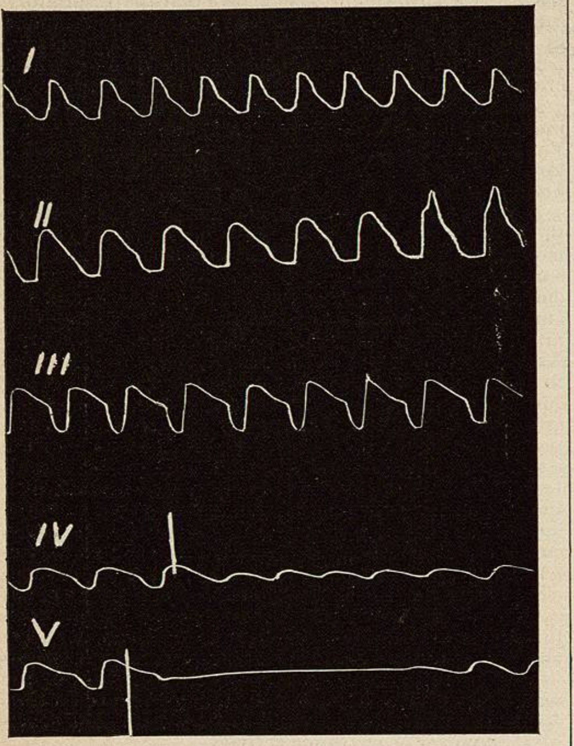

FIG. 4109.—Illustrates the Action of the Vagus on Respiration. Taken by the writer with an apparatus like that shown in Fig. 4107. *I*, Normal breathing of rabbit under ether; *II*, both vagi cut, respiration deeper and slower; *III*, cerebral hemispheres removed also; *IV*, weak stimulation of vagus opposite vertical line showing shallowing and quickening; *V*, stronger stimulation showing complete inhibition. Note: Downstrokes, inspiration; upstrokes, expiration.

other. The result is that the body of No. 1 and the brain of No. 2 receive the same blood and *vice versa*. If now the respiratory interchange of No. 1 be interfered with, the blood supplying his body will become venous, but his brain will continue to receive arterial blood from the other dog and his breathing will be unaffected. Dog No. 2, however, whose brain receives venous blood, will become dyspnœic, although the rest of his body is receiving good arterial blood.

Certain substances, other than carbonic acid, are produced in the muscles during activity, substances which also increase the activity of the respiratory centre. It has been shown that various acid substances have this effect, and the unknown substances formed in muscle are probably acid in nature.

The so-called automatic activity of the respiratory centre is believed to depend on a stimulus received from the blood, but it is yet undetermined whether the most important factor in this stimulus is a deficiency of oxygen, the presence of carbonic acid, or the action of the acid products of metabolism, although much can be said in favor of the last named.

The Influence of Afferent Nerves.—There is only one pair of nerves which have a tonic influence on the respiratory centre, as shown by a change in respiration when they are cut. These are the pneumogastrics.

On cutting one vagus (pneumogastric) the breathing becomes slightly deeper and slower for a time. Later the effect may pass off and the breathing become normal again. If both vagi are cut, the deepening and slowing of the breathing is more pronounced and the effect is more lasting.

The effects of stimulating the central end of one vagus are differently described by different writers. Nearly all agree that weak stimulation frequently produces shallowing and quickening, so that the breathing becomes more or less like what it was before the nerves were cut. With stronger stimulation various results are obtained according to the way in which the experiment is carried out, being influenced by the employment of anæsthetics and to some extent by the kind of stimulus used. This being the case, some writers believe that the pneumogastrics carry impulses which stimulate the respiratory centre to increased activity: and others, among whom is the writer, believe that it carries principally inhibitory impulses.

The impulses which normally ascend the vagus, exercising a constant inhibitory influence on the respiratory centre, are dependent upon the lung being distended, for Loewy has shown that opening the pleural cavity on one side so as to allow the lung to collapse has exactly the same effect on respiration as cutting the vagus on that side.

By rapidly inflating the lungs with a bellows the breathing may be entirely inhibited, the condition known as *apnœa* being produced. The result follows, no matter whether air be used for inflation, or some neutral gas, such as hydrogen. If air be drawn out of the lungs, diminishing their distention, very deep inspirations result. Hering and Breuer, who obtained these results, and also Head, who repeated their experiments, endeavor to explain them on the assumption that there are two kinds of fibres in the vagus, of which one set brought into action by distention of the lung favors expiration, and another set acting when the lung is collapsed favors inspiration. Their results are far more simply explained in the light of Loewy's work, by saying that the moderate distention of the lung normally present causes weak inhibitory impulses to ascend the vagus, which control the respiratory centre; increased distention gives rise to stronger impulses, which inhibit it altogether and produce a condition of apnœa; while during collapse of the lung the centre acts more powerfully in the absence of the usual inhibitory impulses.

In considering the effect of stimulating the fibres of the vagus directly we must remember that besides the respiratory fibres proper we can have passing up the vagus impulses of general sensibility and of pain, and these may cause changes in respiration through the sensorium like any other afferent nerve. The more completely we prevent the animal from feeling pain, the less likely are we to get pain effects and the more certain to see the direct action of the vagus on the respiratory centre. If an animal be experimented on without being completely narcotized, artificial stimulation of the vagus may produce almost any imaginable effect on the breathing, either inspiratory spasm (gasp), expiratory spasm (cry), or inhibition. If, on the contrary, the animal be well anæsthetized or decerebrated pain effects are eliminated and pure inhibition is nearly always seen, as shown by shallowing and quickening with weak stimulation, passing gradually, as the stimulus is increased in strength, into a state of complete inhibition or standstill in a position intermediate between inspiration and expiration (see Fig. 4109).

Even in unnarcotized animals the ascending constant current which stimulates without causing pain has almost always an inhibitory effect.

The other afferent nerves have no tonic action on the centre, for cutting any of them does not produce any change in the breathing. In special emergencies any afferent nerve may carry impulses that modify the action of the centre. If the nasal mucous membrane (fifth cranial nerve) be stimulated we get a *sneeze*, consisting of a gradual inspiration followed by a sudden spasmodic expiration through the nose. If the *glossopharyngeal* nerve be stimulated, as in swallowing, we get inhibition of respiration, which prevents food being drawn into the

larynx. Certain kinds of stimuli applied to the mucous membrane of the pharynx and tonsils cause the complex act of vomiting in which the muscles of respiration play a part. Stimulation of the *laryngeal* nerves causes in some cases mere slowing of the breathing; but if the stimulus be strong, we see inhibition of inspiration and expiratory spasm or cough. Stimulation of the *splanchnics* inhibits respiration. Stimulation of the optic or auditory is said to increase inspiratory activity. Stimulation of other sensory nerves, such as the sciatic, produces in many cases one or more deep inspirations with weak stimulation, and a strong expiration or cry if the stimulation is strong; but the results are by no means uniform.

The Influence of the Posterior Corpora Quadrigemina.—Removal of the brain in front of the posterior corpora quadrigemina has little effect on the breathing; but separation of these from the medulla has an effect just like bilateral section of the vagi; that is, the respiration becomes deep and slow. If the vagi be cut as well and the animal has been protected from excessive hemorrhage the respiration becomes still deeper and very infrequent. Usually in this case inspiration and expiration are separated from each other by long pauses. Restoration of the respiration, to about its normal character, may be effected by a well-chosen stimulus applied either to one of the vagi or to the corpora quadrigemina.

Cheyne-Stokes Breathing.—If the upper part of the medulla itself be injured the breathing is sometimes seen to take on a periodic character; that is to say, the respirations occur in groups of three, four, five, or more, of which the first respiration in each group is the deepest (Markwald), and the groups are separated by intervals in which respiration is in abeyance. A similar kind of respiration is seen when a blood extravasation presses on the region of the alæ cinereæ near the respiratory centre. These facts are interesting in connection with the so-called Cheyne-Stokes breathing occurring in various diseases of the brain, heart, and kidneys, which bears certain resemblances to this experimentally induced periodic breathing (see article on *Dyspnœa*).

The Conditions under which the Centre Acts.—A rational interpretation of all the facts given above would seem to be as follows:

1. The respiratory centre is situated in the medulla, in the lower part of the floor of the fourth ventricle.
2. It receives a constant stimulus from the blood.
3. Acting alone it would expend all its energy by responding at long intervals with a very great respiratory effort.
4. It receives inhibitory impulses from the posterior corpora quadrigemina, and by the vagi nerves from the lungs which control its action and convert the deep infrequent respiratory acts into the shallower and consequently more frequent ones that we know as normal breathing.
5. In special cases the centre may be influenced by impulses reaching it by other nerves.

The Efferent Nerves are the phrenics to the diaphragm, the intercostals, and the motor nerves to the other muscles of respiration. If the spinal cord be injured above the first dorsal vertebra the intercostal nerves and muscles are cut off from the centre and thoracic respiration ceases. If the injury be as high as the fourth or fifth cervical vertebra the phrenic nerves and diaphragm are also cut off from the centre and death ensues.

For the effect of breathing air at various pressures and air containing impurities see articles on *Air*, *Aërotherapeutics*, and *Caisson Disease*. *William S. Morrow.*

REFERENCES.—In preparing this article use has been made of the books of Schaefer, Mills, Foster, "American Text-Book" (Reichert), Hall, Halliburton, Jeffrey Bell, Böhm and Davidoff, Quain's "Anatomy," Hermann's "Handbook" (Rosenthal), Langendorff's "Physiologische Graphik"; also of numerous journal articles and data from experiments performed by myself. Special acknowledgment must be made of assistance received from two papers by Max Lewandowsky in Du Bois-Reymond's Archives for 1896 on "Die Regulierung der Athmung."

RETINA, DISEASES OF.—The retina is seldom affected by disease which is limited to itself alone, or even to the eye alone, but most often lesions of the retina are part of a general disease and are frequently of assistance in the diagnosis of the latter. The diseases most apt to produce serious retinal complications are, diseases of the kidneys, syphilis, diabetes, septicæmia, and leukæmia. Among ocular affections choroiditis and optic neuritis almost always lead to retinal changes, the former because of the close anatomical relationship of the choroid and retina, and the latter on account of the interference of the retinal blood supply produced by the swelling of the disc. Both choroiditis and optic neuritis, however, are usually in turn dependent upon some general disease.

VASCULAR DISTURBANCES OF THE RETINA.—*Pulsation of the retinal veins* on the disc is frequently seen under normal conditions, and can readily be produced by a slight pressure of the finger upon the eye. It is particularly associated with increased intra-ocular tension from any cause, and hence is common in glaucoma. No better explanation of the phenomenon than that of Donders has been advanced. According to Donders it is due to the changes in arterial tension being communicated to the veins through the vitreous humor. True transmitted venous pulsation has been seen in valvular heart disease, arteriosclerosis, and anæmia, but never under normal conditions.

Pulsation of the retinal arteries is always pathological, and indicates either an increase in intra-ocular tension or decrease in the arterial pressure. It may occur in glaucoma, anæmia, syncope, senile arteriosclerosis, aneurism of the arch of the aorta, aortic insufficiency, and Basedow's disease. It may also result from compression of the central artery by tumors of the nerve or orbit.

Hyperæmia of the retina may be either arterial or venous in nature. The general redness of the fundus depends to such a great extent upon the degree of pigmentation of the choroid, and the tortuosity of the vessels varies so much under normal conditions, that it is impossible to diagnose retinal hyperæmia unless the disc is also reddened. *Arterial hyperæmia* manifests itself by distention and tortuosity of the arteries which sometimes lie in antero-posterior planes so that they project toward the observer. It may result from eye strain due to improper illumination or errors of refraction, irritation of the eye from any cause, such as the presence of a foreign body on the cornea, and from keratitis, choroiditis, and iritis. It is common in meningitis, and may be noted in Basedow's disease, plethora, and neurasthenia. Strangely enough, it may result from excessive loss of blood or from chlorosis, and in the former case it may be so intense as to give rise to retinal hemorrhages. *Venous hyperæmia* is characterized by dilatation and tortuosity of the veins, which appear darker than normal, and is always associated with hyperæmia of the disc. It is not infrequently accompanied by retinal hemorrhages. The arteries may show no change, or they may be narrowed owing to the same obstruction which is producing stasis in the veins. In general, venous hyperæmia is due to some hindrance to the outflow of venous blood from the eye, as, for instance, to compression of the central vein in optic neuritis or glaucoma. Sometimes the obstruction lies in the orbit, as in cases of tenonitis and orbital cellulitis, or even in the cranial cavity, as in intracranial tumors, thrombosis of the cavernous sinus, and meningitis. Rarely it is a part of a general venous stasis due to valvular heart disease. A few cases of particularly exaggerated venous congestion have been seen associated with congenital heart disease, the condition then being spoken of as *cyanosis retinæ*.

Thrombosis of the central vein of the retina, which produces the highest grade of venous hyperæmia, is very rare. It usually is monocular and occurs in patients affected with general arteriosclerosis, and hence most often between the ages of sixty to seventy, but sometimes it occurs as the result of orbital cellulitis. The affection comes on suddenly without prodromal symptoms, and though vision is much diminished, blindness