thus, a single injection of as small an amount as $\frac{1}{4}$ m. has sometimes proved sufficient in the former case (for example, Fig. 5), while in the latter from 1 to 2 m. are necessary to produce any effect, and usually three or four injections of 1 m. each must be given before the animal ceases to breathe. It is worthy of notice that the primary fall of blood pressure which occurs in many cases upon injection into the vertebral is seen only when the amount injected is small, such as $\frac{1}{4}$ m.; with larger doses, such as 2 m., the blood pressure rises immediately after the injection.

In many cases when the injection is made into the carotis, a well-marked slowing of the heart occurs soon after the injection, and it is striking to see how these slow beats of the heart are unable to lower the blood pressure, owing to the simultaneous stimulation of the vasomotor centre, as is well shown in Fig. 3 c. In this case the slowing of the heart observed cannot be attributed to stimulation of the vagus nerves, for both vagi were cut before the chloroform was injected into the carotis. In other instances where well-marked slowing was obtained in consequence of chloroform administration, such slowing was undoubtedly due to vagus stimulation, for the effect was dependent on the integrity of the vagi. We have, however, observed in the course of our experiments many instances similar to the one quoted, where undoubtedly, owing to the fact of previous section of the vagi, some other explanation must be found; and careful measurement has shown us that in the majority of such cases of slowing, the rate of beat was diminished to exactly half the immediately preceding rate, as in the instance quoted. This suggests very strongly that the slowing in question is an indication of a partial block between auricle and ventricle, in consequence of which the ventricle responds only to every second auricular contraction, a phenomenon which is well known to occur in the hearts of both cold- and warm-blooded animals. We have observed this peculiar form of slowing under many different circumstances, but have not yet been able to make up our minds as to the paramount condition for its occurrence; in some cases it has appeared to be associated with an asphyxial condition of the blood; it certainly is not necessarily dependent on the presence of chloroform in the blood, for we have never observed it after the injection of chloroform into the jugular. It is not advisable to discuss the question further in this place, but we hope to be able to throw further light upon the causation of such a dropping of beats upon a subsequent occasion.

CHLOROFORM APPLIED TO FOURTH VENTRICLE.

Finally, to finish up with the effects produced by the direct action of chloroform on the nervous centres, we have found that the respiration can be easily stopped by the direct application of one or more drops of chloroform to the fourth ventricle of the brain. We have not as yet made a sufficient number of such experiments to enable us to discuss the differences observed in connection with the differences of effect of the carotis and vertebral injections.

It is remarkable how small an effect is produced on the anæsthetised animal by the opening of the atlo-occipital membrane; a large amount of cerebro-spinal fluid runs out as a rule, yet neither the respiration or the blood pressure is appreciably affected; when the chloroform is first applied muscular movements often occur and the respirations are increased in depth and frequency. Upon the application of a second drop no movements of the animal take place as a rule, but the respiration is temporarily quickened and increased. The cessation of respiration takes place gradually, not suddenly; the diaphragm contractions become weaker and weaker, and finally cease. At the commencement of this weakening each contraction for some time is apt to be lengthened as in the case of carotis injections. The paralyzing effect on the respiration of the chloroform, when applied to the fourth ventricle, is its most striking effect, and is in marked contrast to the action of such a stimulant as nitrate of silver, which, according to Gad,⁵ does not stop respirations when applied to the fourth ventricle.

The effect on the blood pressure is not well pronounced, as far as can be judged from the few experiments we have made; in some cases there is a slight primary fall followed by a slight rise; in others a rise only, without any preliminary

fall. The respiratory blood pressure curves are apt to be very well pronounced, and the gradual fall which takes place with the gradual cessation of respiration is not broken by an asphyxial rise. Periodic undulations resembling Traube-Hering curves were not observed as the result of the application of chloroform to the fourth ventricle.

From these experiments we may draw the conclusion that chloroform, whether injected into the cerebral arteries, or applied directly to the medulla oblongata, first stimulates, then paralyzes the parts of the brain with which it comes in contact: thus the stimulation of the respiratory centre is shown by increased frequency and force of the contractions of the diaphragm strip; these last but a very short time and then the respiratory movements become slower and weaker or slower and longer up to complete cessation, or cease somewhat suddenly. The stimulation of the cardio-inhibitory centre may be shown by the occurrence of heart slowing dependent upon the integrity of the vagus nerves; this effect also is seen only for a short time after injection. The stimulation of the vasomotor centre is shown by the marked rise of blood pressure, which continues for a long time and gives way ultimately to a paralysis, as shown by the absence of any asphyxial rise of pressure after respiration has ceased, and also by the absence of any reflex rise of pressure upon stimulation of a sensory nerve. Perhaps also the presence of the periodic undulations resembling Traube-Hering curves indicates the action of a strong stimulus upon a less excitable centre, as seems to be the case in many instances of periodic rhythmical activity of the central nervous system.

(To be continued.)

REPORTS TO THE SCIENTIFIC GRANTS COMMITTEE OF THE BRITISH MEDICAL ASSOCIATION.

A PRELIMINARY REPORT ON CEDEMA.

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SINCE the process of transudation is essentially a vital one, it will long remain a fertile source of inquiry to the physiologist; it is still more important to the pathologist. The passage of fluid from the circulating blood through the wall of the blood vessel into the cell spaces and then into the capillary lymphatics was supposed by Lower in 1669 to be due to mechanical pressure in the blood vessels produced by venous stagnation. This idea has survived to the present day. As a matter of fact, of course, the complex processes of living tissues are not to be so easily explained by the simple statement of Lower. Two hundred years after Lower (namely, in 1869) Ranvier proved that another factor must be considered, namely, the action of the nervous system. We will subsequently return to the discussion of his facts, which have received scant attention in this country.

Enumeration of Various Factors in the Production of Edema.
—Twenty years after Ranvier we have the remarkable researches of Heidenhain, in which the concurrence of the various factors is first stated comprehensively, in a thorough and accurate analysis. Being responsible in lecturing on general pathology for giving a reasonable exposition of this commonly supposed simple subject, we have always felt the necessity of setting on foot further investigation of the questions it involves. Having with this object entered on a research of this kind, we intend on this occasion to refer only to certain points that may be readily illustrated, and to for-

⁵ *Verhandl. der physiol. Gesellsch.*, 27th June, 1890.

mulate, if possible, the distinct questions which are really embodied in the single word "œdema." Stated categorically, the several divisions of the subject on which information must be obtained are as follows:—

1. The chemical and morphological constitution of the blood.
2. The condition of the so-called vasoconstrictor spinal nerve centres.
3. The condition of the peripheral vasomotor centres.
4. The condition of the peripheral vasomotor nerve fibres.
5. The possible existence of vasotropic nerve fibres.
6. The possible existence of vasosecretory nerve fibres.
7. The condition of the nerve endings of the fibres named in 4, 5, and 6.
8. The condition of the endothelium of the blood vessel wall.
9. The condition of the other tissues of the blood vessel wall.
10. The condition of the ground substance and cell spaces.
11. The condition of the connective tissue corpuscles.
12. The condition of the nerve fibres and nerve endings in relation with the connective tissues.
13. The condition of the endothelium of the lymph vessel wall.
14. The condition of the other tissues of the lymph vessel wall.
15. The condition of the nerve fibres and endings in relation with the lymph vessel wall.
16. The chemical and morphological constitution of the œdema fluid.
17. The chemical and morphological constitution of the lymph.
18. The pressure and rate of flow of the blood.
19. The pressure and rate of flow of the lymph.

It will be seen that in truth the facts of normal anatomy and physiology on several of these points are wanting.

The Insufficiency of Physical Theories.—We believe, however, that it will not be useless to state what remains to be done as well as to discuss what has been accomplished. In the first place, as regards the possibility of finding an explanation of the phenomena in simple physical considerations. It is not going too far to assert that the remarkable paper by Tigerstedt and Santesson¹ disposes, once and for all, both of the conclusions that have been derived from physical considerations, and of the claim that the process of transudation in the living body is capable of interpretation by mere variations of pressure on the sides of a permeable membrane.

What is Venous Stagnation?—It is essential that we should formulate our views on this matter, since no greater error exists than that as regards this oft-spoken-of factor. Since venous anastomosis is so free, it is self-evident that the term "venous stagnation" must always be relative and not absolute. Not only is this to be considered so far as the mere distension of the vessel is concerned, but also as regards the part or tissue in which the stagnation is occurring. Of these two points we will now give examples drawn from our experiments.

The Proportionate Degree of Distension.—In a dog in which Ranvier's experiment of retroperitoneal ligature of the vena cava and concurrent section of the sciatic nerve was performed, no œdema whatever occurred, not even in the thigh. Moderate enteritis was present, but on killing the animal the remarkable and, according to Professor Ellenberger, who kindly wrote to one of us on the point, rare anomaly of a double vena cava, was found. Venous stagnation here, therefore, must have been very low in consequence of the unforeseen anastomosis. There was a remarkable turgidity of the fat about the bladder, which is a very constant lesion after the ligature of the cava. The degree to which this is developed is conceivably proportional again to the same thing—namely, freedom of anastomosis—but also to the looseness or distensibility of the tissue involved. Further evidence in favour of the former of these views is shown by the fact that in the female, in whom of course the anastomoses are very free, and the ovarian and uterine veins large, this turgidity of

the perivesical fat is rarely marked, whereas it is at its acme in the male.

The Influence of the Nervous System.—Ranvier's experiment consisted in ligaturing the vena cava between the spermatic and ilio-lumbar trunks. This operation and that of ligature of the femoral and iliac veins is commonly considered by clinicians to be necessarily a fatal obstruction and the source of intense œdema, even in cases where the vessel walls are healthy. No œdema occurs in dogs with this profound venous stagnation unless, as Ranvier showed, section of the vasomotor nerve fibres is superadded. In an animal so experimented on, very marked œdema is produced in the right leg in which the sciatic nerve was divided; whereas the left leg remained free from it, although, of course, the seat of equal stagnation. As regards the accuracy of Ranvier's dictum, which has been adversely criticised by Sotnitschewsky, it ought here to be said that of twelve such experiments we have seen Ranvier's result in nine. There is no doubt, therefore, that, as Ranvier stated, in dogs this combinations of factors produces œdema. In cats and rabbits, as Sotnitschewsky² points out truly, we find the phenomenon is not nearly so marked. The actuality of the œdema thus evoked is well shown by dissection; a rapid dissection of the ankle region exhibits well the infiltration of the loose tissues about the tendo-Achillis, and another, similarly prepared, the distension of the areolar spaces and separation of the component fibres.

The Chemical Condition of the Blood.—The late Dr. Wooldridge was the first to show that the condition of the albuminoids of the blood, especially the fibrinogens, could be profoundly altered by the injection into the circulation of certain other albuminoids which he termed *tissue fibrinogens*. The clinical action of these substances is to produce a twofold effect, [namely, (1) intravascular clotting; (2) a negative phase, namely, non-coagulability of such blood as may have escaped clotting. A small dose of such albuminoids, he discovered, led to the occurrence of œdema or dropsy, and extravasation of red blood corpuscles, when the altered blood was circulating through a district of tissue in which the blood vessels were moderately distended. Thus, if the femoral vein be tied, no œdema follows, but if Wooldridge's tissue fibrinogen be concurrently injected, then, as is shown in our experiments, the occurrence of œdema is very obvious. In this combination of factors again, as in Ranvier's experiments, we are dealing with the vessel wall on the assumption that it is healthy and unimpaired. Now, as Wooldridge first showed, the disruption of the normal relation between the circulating living plasma and the vessel wall is not only a point of profound physiological importance, but is also relatively readily brought about by the injection of the substances termed by him "tissue fibrinogens."

The Relation of the Vessel Wall to the Blood within it.—We would venture in this sketch to allude to the behaviour of endothelium when it is the seat of pathological transudation. Arnold showed long ago that the stigmata and pseudostomata, as described by Dybkowsky, Schweiggerseidel, Cohnheim, Klein, and Sanderson, and a host of observers both previously and subsequently, are definitely increased in size when the influence of œdema or of exudation exciting agencies is brought to bear on the vessel. In animals in which, owing to the injection of the tissue fibrinogen, thrombosis and transudation were in active development, the epithelial covering of the pulmonary pleura showed very marked pseudostomata.

Cellular Secretory Action.—It is impossible to conclude even a sketch of this kind without reference to Heidenhain's view of the secretory action of the endothelial cells of the blood-vessel walls, and probably also of the connective tissue corpuscles. We have as yet no new facts on this subject to offer; but we would refer to the table of points which must be investigated, to suggest if possible the way in which the fruitful suggestions of Heidenhain should be followed out. Mr. White has very kindly agreed to pursue the research so far as the changes in the blood and lymph vessel walls are concerned. It would be very gratifying if possibly concomitant investigation could be commenced on the various lines not at present in the hands of physiologists and pathologists, so that the elucidation of this important subject might be substantially pushed forward in relatively a short time.

¹ *Mittheilung vom Physiolog. Laborat. des Carol. Med. Chir. Inst. in Stockholm, 1886; Bihang vid k. Svenska Vet. Akad. Handlingar, Band II, No. 2, June 6th, 1885.*

² *Virchow's Archiv, Bd. 57, p. 55.*