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THE PHENOMENA OF ACIDOSIS AND ITS DOMINATING INFLUENCE IN SURGERY*

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LIFE is incompatible with acidity, for not only animal but plant life as well demands for its continuance an alkaline or at least a neutral medium. When soil becomes acid it must be "fertilized" by the addition of alkalies, or it becomes sterile. Water plants cannot grow in acidulated water, and if the alkalinity of the blood in animals be even slightly diminished life ceases.

It is, however, by the breaking down of alkalies and bases that energy is produced for muscular action and heat, that is, for the phenomena of life itself, and the breaking down of alkalies and bases is invariably attended by the formation of acid by-products. If the soil, the sea and the blood must be alkaline in order to support life, and if the activities of life are constantly producing acids, by what means are the acid by-products of energy transformation neutralized? The acidity of the soil is removed by man by the addition of fertilizing mixtures; the plants rid themselves of their acid by-products by diffusion into the soil through their roots; for man, however, a special mechanism of neutralization and elimination is required.

On *a priori* grounds one would expect that part of the mechanism evolved in the human body for the elimination of acids would be adapted to eliminate the gaseous acids and another to eliminate the acids in solution.

The elimination of gaseous acid, CO_2, is obviously principally accomplished by the lungs. The maximum ventilation of the lungs is attained by rapid and deep respiration; by wide dilatation of the nostrils, the bronchioles and the air vesicles. Dilatation of the alæ nasi, of the bronchioles and of the air vesicles is governed by adrenin, while the rate and amplitude of respiration is under the control of the respiratory

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centre in the medulla. An increase of CO_2 in the body must therefore cause an increased output of adrenin, and must increase the activity of the respiratory centre.

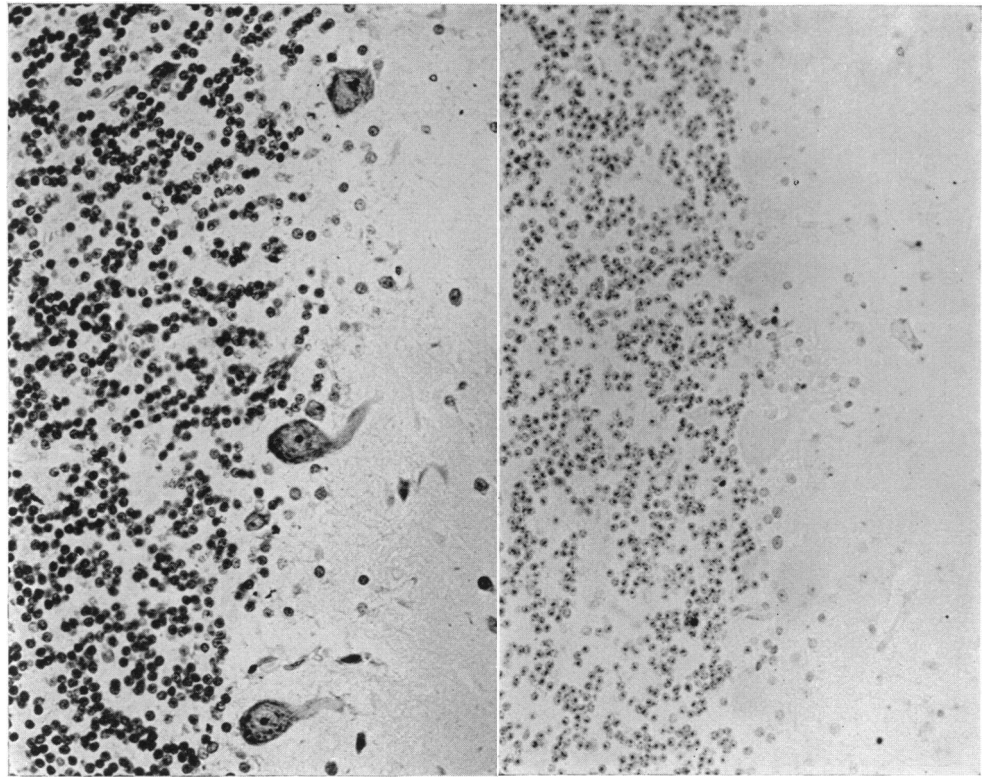
Magnus, Elliott, Cannon and myself have shown that exertion, emotion, injury, infection, auto-intoxication, Graves' disease, strychnine convulsions, injections of indol and skatol, of amino-acids, of foreign proteins, of placental extract—in fact all the activators of the mechanism for energy transformation, cause an increased output of adrenin. We have shown also that all these activators cause increased acid by-products, both gaseous and in solution. The adrenals are controlled by the brain, and when the connection between the brain and the adrenals is severed, or when the function of the brain is depressed or suspended by morphia, then activation of the adrenals causes no increased output of adrenin. Physiologists are now agreed that the H-ion concentration of the blood governs the respiratory centre.

These facts show that the mechanism for the elimination of the gaseous part of the acid by-products of energy transformation—metabolism—consists of the brain, the adrenals and the lungs. That is, the presence of carbon dioxide in the blood stimulates the centres of the brain which govern the rate and the amplitude of respiration and that which governs the output of adrenin. Therefore, the injection of CO_2 in a normal individual should cause increased adrenin output and increased respiration—and by experiment we have proved that it does so. The injection of carbon dioxide alone causes no other symptoms.

It is of immense significance that the vital function of the respiratory centre is controlled by the H-ion concentration of the blood. The mere fact that the H-ion concentration rather than oxygen controls the respiratory centre shows, in fact, that the life of animals is more endangered by increased acidity than by decreased supply of oxygen.

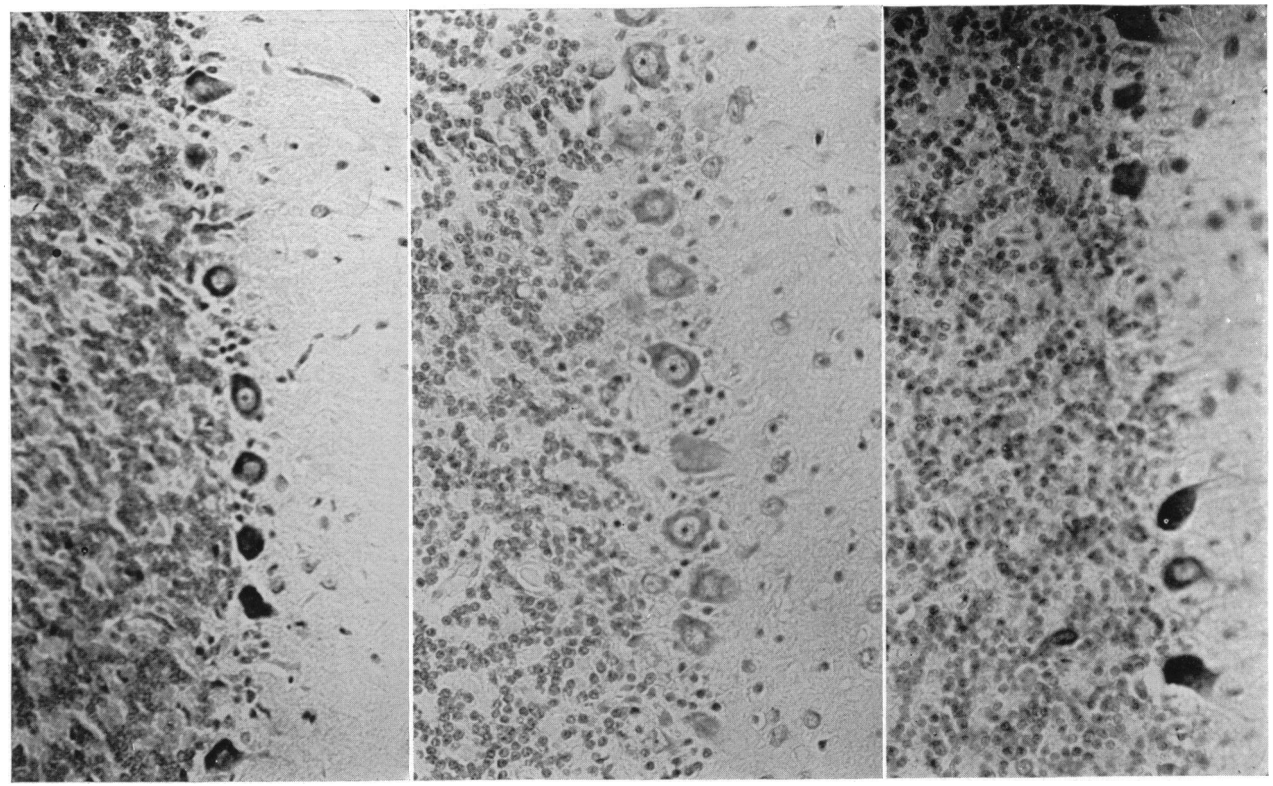
The final points of exit from the body for the acid by-products which are in solution in different body fluids are the kidney tubules and the sweat-glands. The acid by-products of energy transformation when first formed, however, are not in a chemical form suitable for elimination by the kidneys or the skin, but must first be transformed into harmless salts, such as phosphates, sulphates, chlorides, urea, creatin, and creatinin. In these forms acids may be eliminated without harming the kidneys.

It is necessary, therefore, to discover where the chemical substance or substances which transform the harmful acid by-products of metabolism into harmless acid salts are stored; what mechanism regulates



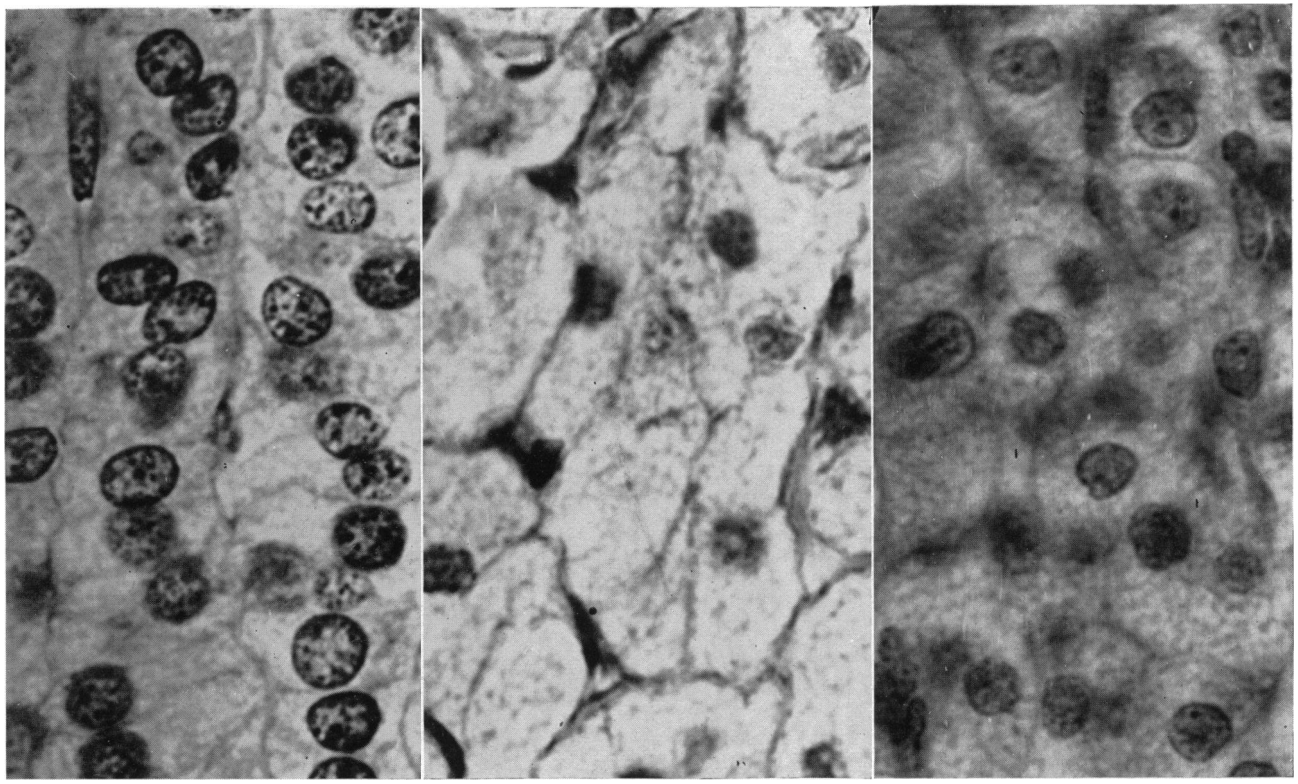
A *B*

FIG. 1.—*A*, Section of human cerebellum—normal (x 310). *B*, Section of human cerebellum showing effect of acidosis (x 310). There are no active cells present, but faint traces of the Purkinje cells are visible.



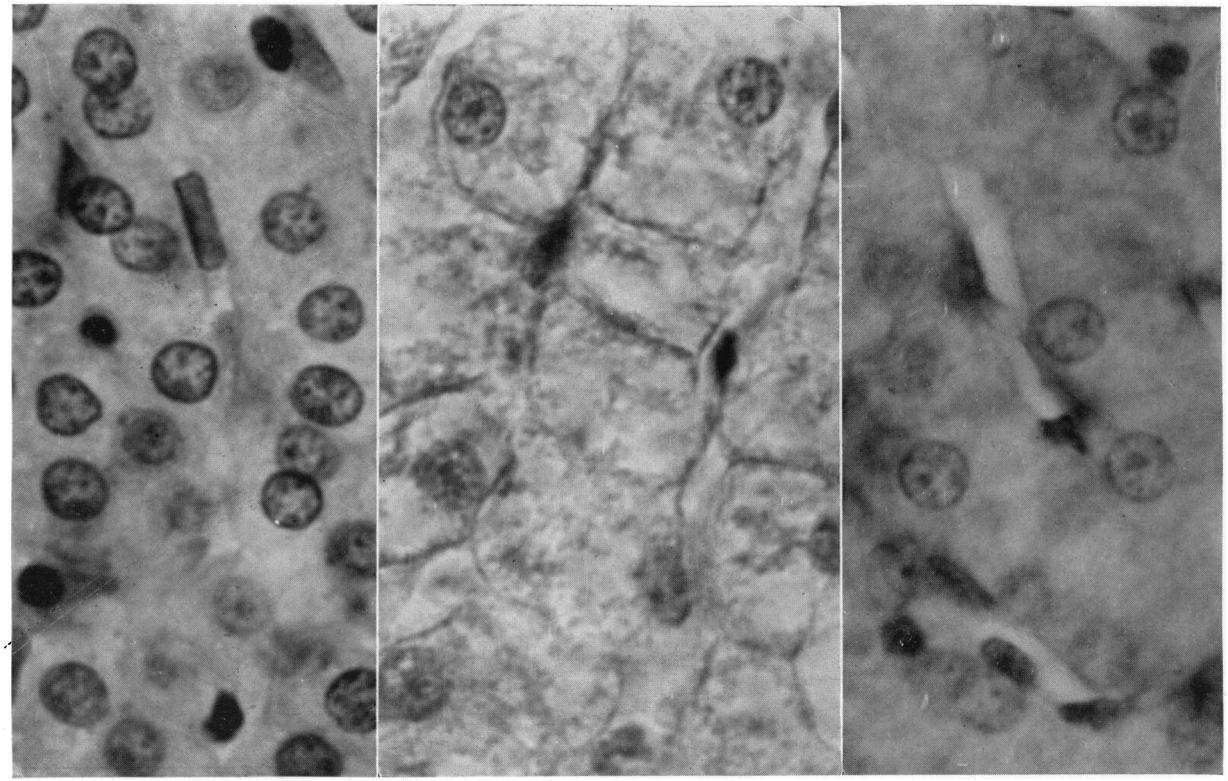
A *B* *C*

FIG. 2.—*A*, Section of cerebellum of cat—normal (x 310). *B*, Section of cerebellum of cat showing effect of injection of acid sodium phosphate (x 310). Compare the destructive effect of the acid with the protective effect of the alkali in *C*. *C*, Section of cerebellum of cat showing effect of injections of sodium bicarbonate (x 310).



A *B* *C*

FIG. 3.—*A*, Section of normal adrenal of cat (x 1640). *B*, Section of adrenal of cat showing effect of injection of acid sodium phosphate (x 1640). Note the disappearance of cell substance, the misshapen cells and eccentric nuclei. *C*, Section of adrenal of cat showing effect of injection of sodium bicarbonate (x 1640). Compare the protective effect of the alkali with the destructive effect of the acid in *B*.



A B C

FIG. 4.—*A*, Section of liver of cat—normal (x 1640). *B*, Section of liver of cat showing effect of injections of acid sodium phosphate (x 1640). Note the general disappearance of cell substance and the vacuolated spaces. *C*, Section of liver of cat showing effect of injections of sodium bicarbonate (x 1640). Note the protective effect of the alkali as compared with the destructive effect of the acid in *B*.

the supply of these substances; and whether the stimulus that activates the mechanism by which energy is transformed into muscular action simultaneously activates the mechanism by which the acid by-products resulting from energy transformation are neutralized or transformed.

In my laboratory we have endeavored to answer these questions both by chemical and by histologic studies. Examinations of all the organs and tissues of the body after the application of every kind of kinetic stimulus showed histologic changes—disappearance of chromatin and changes in the size and shape of the cells—in the brain, the adrenals and the liver, and in these organs only. Moreover, the injection of an acid, such as acid sodium phosphate or hydrochloric acid, caused identical lesions, while the injection of an alkali—sodium bicarbonate—caused no histologic changes in the brain, the adrenals and the liver excepting to increase their stainability. Chemical studies showed a diminished percentage of glycogen in the muscles after the application of kinetic stimuli and consistent changes in the iodine content of the thyroid and of the glycogen content of the liver as well. Our chemical studies showed further that all the fluids in the body excepting the urine are alkaline and that the blood, the spinal fluid and the bile are persistently alkaline, and that the *potential alkalinity* of each is great, that is, that each has a high power of acid neutralization.

For the further identification of the organs governing acid neutralization studies of the H-ion concentration of the blood were made after the excision of different organs. The excision of the pancreas, of the spleen, of the thymus, of the thyroid, of the testicles, of the ovaries, of portions of the intestines, of the stomach and of the brain caused no change in the H-ion concentration of the blood; but the excision of the adrenals or of the liver was followed by increased H-ion concentration before death.

That is, in from four to eighteen hours after excision of the adrenals the alkalinity of the blood began to decrease, and coincidentally with this decrease in alkalinity began the rapid decline of the animal. Excision of the liver was followed by death in from a few to sixteen hours, and just before death the H-ion concentration of the blood rapidly increased. Histologic studies of the organs of these animals showed, in the case of the animals which had undergone adrenalectomy, a marked deterioration of the cells of the brain and the liver, and in the animals whose livers had been removed the brain and the adrenals showed extensive histologic changes.

All of these studies determine that the brain, the adrenals, the liver, the thyroid and the muscles together play important parts in energy

transformation, and that at least three of these organs, the brain, the adrenals and the liver, are especially concerned also in the neutralization of the acids resulting from energy transformation.

What is the function of the brain in acid neutralization? The evidence already given suggests that its part is to govern the mechanism by whose action the actual neutralization is accomplished. The following experimental observations further establish this fact. When the H-ion concentration of the blood of an animal had been increased to the point of actual acidity even—by emotion, exertion, or anæsthesia—and the animal was then deeply morphinized, it was found that the blood did not return to its normal alkalinity, that is, the body had lost the power to neutralize acidity. The clinic also has confirmed the fact that heavy morphinization hinders or even inhibits the neutralization of increased acidity caused by anæsthesia.

In addition a decapitated animal in which the H-ion concentration had been increased by anæsthesia or by strychnine convulsions showed but slight power of overcoming the acidity.

We conclude, therefore, that the brain performs a dual kinetic function—its driving power is the principal cause of the transformation of energy, and it has also evolved within itself a mechanism for the neutralization of the acid products of energy transformation.

In addition to the active functions of the brain, the adrenals and the liver in acid neutralization, the body fluids have an inherent form of neutralization independent of the brain.

If after excision of the brain the H-ion concentration of the blood is increased and adrenin administered, the neutralizing power of the body will be increased. If the liver as well as the brain be removed, however, the neutralizing power of adrenin will be lost.

If our conclusions be well founded, they provide us with the key to the causation of certain conditions and to the interpretation of certain clinical phenomena. For example, if in a certain case there is shown a continuous increase of acid by-products for the neutralization of which an unusual amount of alkali is required, then we may presume that the liver, the adrenals and the brain are undergoing abnormal changes; and that unless the acid condition be altered, these structural changes in the brain, the adrenals and the liver will become permanent and certain of the chronic diseases will result.

For the practical application of this study in my laboratory we are now measuring the acidity of the urine, blood, cerebrospinal fluid and bile by means of indicators—using with some modifications the methods of Sörensen, Henderson and others. In the case of urine and cerebro-

spinal fluid the indicators may be directly applied—the method being made applicable to blood by rapid dialysis by Rowntree's method.

We employ two indicators: (1) sodium alizarin sulphonate (2 per cent. solution) and (2) phenolsulphonephthalein (0.6 per cent. solution). This gives a wide range of H-ion concentrations varying from $P_H = 8.7$ on the alkaline side to $P_H = 4.57$ at the acid end of the scale, the neutral point being $P_H = 7.0$.

(It is customary to express H-ion concentrations in the way suggested by Sörensen, by the logarithm of the H-ion normal with the negative sign omitted—this being indicated by the symbol P_H.)

For making up the scale of standard solutions four stock solutions of known H-ion concentration are prepared:

(*a*) Sodium acetate .....27.2 gms. per litre.
(*b*) Acetic acid .....27.2 gms. per litre.
(*c*) Disodium phosphate .....17.8 gms. per litre.
(*d*) Monopotassium phosphate .....13.6 gms. per litre.

To make up the standard solutions from which the color scale is made, these stock solutions are mixed in varying proportions to yield solutions of the desired H-ion concentrations. For example:

20 c.c. stock solution (*a*) + 30 c.c. stock solution (*b*)
+ 250 c.c. distilled water = A solution, $P_H = 4.57$

The scale is made up by placing about 5 c.c. of each of the standard solutions plus one drop of each of the indicators in an equal number of hand-glass test-tubes of uniform size, then diluting the contents of each tube to about 15 c.c.

The H-ion concentration of any fluid may be quickly found; therefore, by placing about 2–3 c.c. of that fluid in a clean test-tube, adding a drop of each of the indicators, diluting the contents to about 15 c.c. and finding the solution in the scale which most closely matches it in color. The known H-ion concentration of that solution will be the H-ion concentration required.

For the dialysis of blood and of turbid urine collodion membranes are made. The solution to be dialyzed is placed in one of these membranes which is then lowered into a short tube containing normal saline solution at body temperature. This is kept at 37° C. for a few minutes, the dialysate poured off and the H-ion determination made after cooling to room temperature.

This in brief indicates the method by which we are securing new light upon clinical problems.

We can sometimes foresee an impending acidosis. We can check

up the results of operative procedures. We can see the trend of a case in which a condition of mild acidosis already exists, and may discover means by which to ameliorate the physical changes which are caused by or are incident to the presence in the system of abnormal amounts of acid. These observations explain also the reason for what has long proved an advantage in these cases—the use of sodium bicarbonate, and the ingestion of large quantities of water. Just as the acid soil needs water, so does the acid animal body need water.

Whenever there is increased acidity in the body there is thirst. When one exercises he is thirsty; as he is also if he has a fever or is in emotional stress. Anæsthesia is followed by thirst, and we have proved that anæsthesia always produces acidity. Acidosis is accompanied by sweating. Sweating is nature's attempt to aid the kidneys and the lungs in their effort to eliminate acids. An increase in pulse-rate is another phenomenon of acidosis and we have already discussed the function of the increased respiratory rate caused by increased H-ion concentration.

We see, therefore, that the principal phenomena of many normal processes and of many disease processes are due to the activation of the mechanism in the body by which acids are eliminated.

Consider, for instance, the phenomena of ordinary fever, or of infection of any kind. The prominent characteristic clinical phenomena in any case are due to the effort of the body to maintain the normal alkalinity of the blood. The same thing is true of exophthalmic goitre. Indeed in fatal cases of this intensely kinetic disease the common cause of death is acidosis. The so-called post-operative hyperthyroidism is chiefly acute acidosis.

In the cycles of exophthalmic goitre there are periods of vomiting, of acid breath, of restlessness, of rapid heart action, and of rapid respiration—all characteristic phenomena of acidosis.

The acidosis of surgical shock and of Graves' disease on the other hand is the result of the kinetic driving of the entire system to such an extent that an undue strain is put upon all the organs of elimination. This is the explanation also of the acidosis which results from overwork or from excessive physical exertion. For the same reason also great emotion may produce an acute acidosis. As a result of the strain put upon all the organs of elimination by the general activations, some one—the weakest—may break under the strain and a chronic acidosis will result.

Another interesting and significant fact, proved by experiments in collaboration with Dr. M. L. Menten, is that nitrous oxide, ether, and

chloroform during their administration all produce increased acidity of the blood. In our experiments we have found out recently the additional fact that the acidity of the urine is increased markedly under ether and chloroform—less under nitrous oxide. This finding has a most important significance for the surgeon, as it explains why the administration of the anæsthetic to a starved patient with gastric or duodenal ulcer, for example, may cause death by precipitating the impending acidosis. That acidosis does impend in these cases is well known, and our experiments have shown an increased acidity of the urine of starving dogs.

In view of these observations and generalizations, imperfectly sketched as they have been, we may well conclude that in greater or less degree acidosis is present in every abnormal condition of the body whose origin can be traced to excessive kinetic activations from any cause, and that the maintenance of the normal potential alkalinity of the body is of vast clinical importance. The factors increasing acid by-products—emotion, operative trauma, inhalation anæsthesia, starvation, infection—should as far as possible be controlled by the surgeon. The *anociated* operation minimizes these injuring factors, but the patient should also be protected in advance of operation by giving water, glucose, and sodium bicarbonate, and the post-operative state also may be improved and convalescence hastened by these measures.