INFLUENCE OF INTERNAL SECRETIONS ON BLOOD PRESSURE ETC.

THE INFLUENCE OF INTERNAL SECRETIONS ON BLOOD PRESSURE AND THE FORMATION OF BILE

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In connection with work previously reported (1) on the influence of internal secretions on the formation of bile a study of the blood pressure was made. The object of this was two-fold; to observe the effect on blood pressure of the particular gland substance being studied, and to determine what relation, if any, existed between blood pressure changes and the amount of bile secreted after a gland substance had been administered intravenously. The following gland substances were employed: Mammary, orchic, ovarian, pancreatic, splenic, thymic and thyroid. These were all obtained from Armour & Company. To this list was added solution of adrenalin chloride, prepared by Parke, Davis & Company, and secretin, prepared by a method described in connection with other experiments (2). These were all given by intravenous injection. Nearly all of the experiments were performed on dogs, but occasionally cats were used. A description of the technique will be found in the article to which reference has been made (1) and the numbers of experiments mentioned in this contribution correspond to the experiment numbers there given. All observations were made for arbitrary periods of twenty minutes each. The usual procedure was to record blood pressure and the number of drops of

bile secreted during three twenty-minute periods, one immediately preceding the administration of the gland substance, a second commencing with the beginning of the injection, and a third immediately following the second. In a few cases the third record was not secured. The dose in every experiment, except those with adrenalin and secretin, was 10 mgm. of the gland substance per kilogram of body weight of the animal dissolved in 100 cc. of physiological saline solution. This was warmed to 37°C. on a water bath and injected into the jugular vein by means of a burette. The dose of adrenalin was 0.1 cc. of a 1:1,000 solution of adrenalin chloride per kilogram of body weight, and the dose of secretin was 10 mgm. of a dried acid extract per kilogram.

Adrenalin. Five determinations were made with adrenalin. There was invariably an immediate rise of pressure which averaged 81.25 mm. of mercury. In the case of adrenalin the injections were made much more slowly than with the other substances studied and the maximum to which the pressure was allowed to rise was 220 mm. This high blood pressure, with slight fluctuations, was maintained for five minutes as an average and at the end of the twenty-minute period the pressure had always fallen to or slightly below the original level.

The amount of bile secreted after the injection of adrenalin was always less than during the preceding twenty minutes and the striking feature was the marked

decrease during the period of high blood pressure. For example, in experiment 13 the initial count was 140 drops distributed fairly uniformly throughout the period; during the first five minutes of the injection period one drop was secreted, in the next five minutes three drops, in the third five minutes three drops, and during the last five minutes forty-two drops - a total of 49 drops for this twenty-minute period.

The diminution produced by adrenalin in the amount of bile secreted may be explained by a decrease of both the arterial and venous inflow. As has been shown by Burton-Opitz (3,4) adrenalin injected into the hepatic artery or portal vein exerts a local constricting action and diminishes the inflow and it is not improbable that even when the adrenalin is introduced through a vessel more distant from the liver the same action takes place.

Mammary. Mammary substance was used eight times and in all but one there was an initial rise in blood pressure followed by a fall and a slow return to normal. The average figures for these experiments are as follows: Blood pressure at beginning of injection 109.2 mm.; maximum pressure 117.6 mm., reached 26.4 sec. after injection started; minimum pressure 95.4 mm., 71.4 sec. from beginning of injection; pressure 103.8 mm. at end of first five minutes, and 106.8 mm. at end of period. Experiment 46, which failed to show an initial rise in blood pressure,

was similar in other respects to the experiments of the group. Ott and Scott (5) report a slight fall in blood pressure for a few seconds after intravenous injection of mammary substance but there is no record of the preliminary rise which occurred so uniformly in our experiments.

So far as bile production was concerned the effect of mammary gland substance was not uniform but it would seem to be a temporary decrease. In experiment 11 the falling off in the rate of secretion was most marked immediately after the injection. Twenty-three drops of bile were secreted during the twenty-minute period following the injection as compared with an initial count of forty-six; fourteen of the twenty-three drops came during the last half of the period whereas the original forty-six drops had been quite uniformly distributed. Experiment 8 was similar; the initial count was three drops, but after the injection there was no secretion until the last four minutes of the period when two drops were recorded. On the other hand, experiments 16, 46 and 57 showed a progressive decrease in the formation of bile. The other experiments of the group showed no change or an increased production.

From these records it appears that not only is mammary substance inconstant in its effect on the secretion of bile but that there is no relation between changes in blood pressure and bile formation under its influence.

orchic substance Four showed an initial rise of pressure followed by a fall slightly below normal, a gradual return to the normal level and the pressure at the end of the period approximately the same as at the beginning; two did not show an initial rise, but a slight fall and then a gradual rise above the original level persisting to the end of the period. In one, experiment 4., no blood pressure record was made The average figures for the first group of experiments, viz., 18, 41, 42 and 55, are as follows: Blood pressure at beginning of injection 128 mm of mercury; maximum pressure 147 2 mm , reached 62.5 sec from beginning of injection; minimum pressure 124 mm. at 110.7 sec after injection commenced; pressure at end of first five minutes 134 7 mm., and at end of period 126.5 mm For the second group of orchic experiments, numbers 19 and 62, the initial pressure is 113 mm., followed by a minimum of 99 mm in 20 secs, a rise to 127 mm in 125 sec , 123 mm at end of first five minutes and 132 mm. at the end of the period

The reported observations of the effect of the intravenous injection of testicular extract on blood pressure vary somewhat but agree in general that the pressure is lowered In 1901 Dixon (6) described an immediate and considerable transient fall of blood pressure accompanied by cardiac slowing following the injection of orchitic extract Vincent and Sheen (7) and Miller and Miller (8) note the production of a fall in pressure after testicular

extract. Vincent (9) and Ott and Scott (5) state that the fall in pressure is slight and lasts for a few seconds only. Wheelon (10) records a slight fall in blood pressure after castration Bingel and Strauss (11) were unable to produce a change in pressure by the administration of extract of testis.

Orchic gland substance caused a decrease in the amount of bile formed in five of the seven experiments and in four of these the effect was progressive, a further decrease occurring in the second twenty-minute period after the injection. One interesting feature presents itself in an analysis of these records - there was a primary decrease during the first fifteen minutes following the injection, a rise during the next fifteen minutes, and a second decline beginning about thirty minutes after the gland substance was administered. This second depression of secretory activity was more marked than the first.

A comparison of blood pressure changes with variations in the amount of bile secreted fails to show any uniformity. Of the four experiments showing a rise in blood pressure, then a fall and a gradual return to normal, three gave a decrease in bile formation and one, number 55, an increase of 108.33 per cent. In the two experiments where there was a fall of pressure followed by a rise to a point 18 mm. above the original height at the end of the period the changes in pressure were accompanied by decreased

production of bile in one, experiment 19, and increased production in the other, experiment 62.

Ovary. Ovarian substance was used five times, in four of which blood pressure records were made. Two cases, experiments 20 and 59, showed a rise of pressure shortly after the injection began, then a fall below normal, a second rise above the original level, and a gradual return to normal. Averages: Initial pressure 130 mm. of mercury; first maximum 148.5 mm., 19.5 sec after injection began; minimum 119.5 mm., 44 sec from beginning; second maximum 137.5 mm. at end of first three minutes, and final pressure 132.5 mm. Two other experiments, 43 and 56, with ovarian substance failed to show changes similar to the above, the pressure remaining almost constant. In experiment 5 no blood pressure record was secured.

The effect of ovarian gland substance or extract of ovary on blood pressure has been reported by Ott and Scott (5), Vincent and Sheen (7), Miller and Miller (8), Vincent (9) and Gonalons (12). These investigators agree that the effect is a lowering of blood pressure which is usually slight and transient.

Ovarian substance invariably produced a decrease in the amount of bile formed. The average decrease was 44.59 per cent. in the first period and 59.36 per cent. in the second period after the injection.

Pancreas. This substance was employed in nine experiments and for six of these complete blood pressure records are available. The effects on blood

pressure fall into two groups, one showing a prompt and very marked fall in blood pressure, the other showing a preliminary slight rise followed by a fall. In all of these records there is a rather characteristic lowering of blood pressure which is still in evidence at the end of the period, but from which there is gradual recovery during the second twenty-minute interval Forty minutes after injection the blood pressure averaged 121 mm. as compared with 123.6 mm. immediately preceding the injection.

The first group consists of four experiments, numbers 22, 38, 48, 50, and shows the following: Initial pressure 123.2 mm.; fall began in 5.5 sec. and the minimum pressure, 60 mm., was reached 26.7 sec. from the beginning of the injection. At the end of five minutes the pressure was 86.5 mm., and at the end of the period 95.7 mm.

The second group, experiments 14 and 52, gives these averages: Initial pressure 124 mm.; 17 sec. later pressure began to rise and reached a maximum of 131.5 mm. 19 sec. after the injection was started; then fell to 77.5 mm., 40 sec. from beginning; at end of first five minutes was 118.5 mm., and at end of period 107 mm.

With the exception of Popielski (13), who reports a marked and prolonged rise in blood pressure as the result of the injection of an acidulated watery extract of pancreas, investigators agree that injection of the substance of the pancreas or of saline extracts

of pancreas causes a fall in blood pressure. Ott and Scott (5) state that the lowering of pressure is more marked than that obtained with ovary, testis, mammary, spleen and thymus.

Biliary secretion was decreased in every case in which pancreatic substance was administered. The reduction averaged 45.45 per cent. in the first period and 44.28 per cent. in the second period following the injection. The striking feature in this connection was the great reduction in secretory activity immediately after the injection. The counts made during the periods preceding the injections show the drops of bile falling at a fairly uniform rate. In the first ten minutes subsequent to the introduction of the gland substance only 19 per cent. of the total secretion for the period was obtained, the other 81 per cent. occurring during the second half of the period. In the next twenty-minute period, the second after the injection, the rate of secretion was more uniform but still only a little more than one-half the original.

Secretin. Seven experiments were carried out with secretin. The blood pressure records show an average pressure preceding the injection of 114.1 mm. of mercury; 20.2 sec. after the injection was begun pressure commenced to fall and reachedd a low point of 56.8 mm. 40 sec. from the starting point; at the end of five minutes the pressure was 110.5 mm., and at the end of the period 118.4 mm. In two experiments,

numbers 26 and 54, of this series there was a slight rise of pressure immediately following the injection. This increase above the original pressure averaged 15 mm of mercury, and in experiment 26 was succeeded by a drop similar to that which took place in the other experiments of the group; in number 54 there was no abrupt fall in pressure but a gradual decline with the pressure at the end of the twenty-minute period nearly the same as at the beginning.

The amount of bile produced was greatly increased in every case in which secretin was employed. This increase averaged 241 52 per cent. for the first twenty minutes after the injection and 413 78 per cent. for the second twenty minutes

Bayliss and Starling (14) state, "Acid extracts of the mucous membrane (of the duodenum and jejunum) normally contain a body which causes a fall of blood pressure. This body is not secretin, and the latter may be prepared free from the depressor substance by acting on desquamated epithelial cells with acid." This has been confirmed by v. Fürth and Schwarz (15). Matsuo (16) also concludes that the depressor substance is separate from secretin, especially as acid injected into the duodenum, while producing copious pancreatic secretion, was followed by no change in blood pressure. He was, however, not able to obtain a secretin preparation which did not produce some fall in blood pressure, but the degree of the fall and the activity of the various

preparations were not at all proportionate.

In our experiments it will be observed that while there was, as a rule, a fall in pressure, immediately following the injection this had been recovered from in five minutes and from then on the pressure remained within a few millimeters of the original. At the same time the amount of bile secreted was tremendously increased during the forty minutes the experiments lasted.

Spleen. Injection of substance of the spleen was practically without effect on blood pressure. Seven trials were made and the average pressure prior to the injection was 104.4 mm.; twenty minutes after the injection it was 107.4 mm. Only two experiments showed any fluctuations that could be attributed to the injection. In experiment 21 the pressure rose from 128 mm. to 135 mm. in 20 sec., then fell to 124 mm. 22 sec. later, rose to 136 mm. 63 sec. later, and declined gradually to 129 mm. at the end of the period. The initial pressure in experiment 61 was 130 mm. With the beginning of the injection blood pressure commenced to fall and in 40 sec. had reached 124 mm., from there it rose gradually to 140 mm. at the end of the period.

Ott and Scott (5) report a slight fall in blood pressure for a few seconds after the intravenous administration of splenic substance. Vincent and Sheen (7) and Vincent (9) noted the production of a transient

fall in pressure by splenic extract. Oliver and Schäfer (17) state that spleen produces a preliminary fall of pressure followed by a gradual rise above normal and then a gradual return to normal. Bingel and Strauss (11) found inconstantly a temporary rise of pressure followed by a sharp fall. Miller and Miller (8) state that in their hands saline extracts of spleen invariably caused a rise in blood pressure, which was usually but not always followed by a slight fall below normal.

So far as the formation of bile after the introduction of splenic substance by vein is concerned we found no constant effect. In the first period after the injection four experiments gave a decrease, two an increase, and one no change. Alterations in the rate of secretion during the second period after injection were also without harmony.

Thymus. Five experiments were carried out with thymic substance and no consistent effect on blood pressure noted. Experiment number 39 showed a slight rise in pressure followed by a sharp fall, and a return to normal six minutes after the injection began.

Where any effect on blood pressure was produced by the injection intravenously of thymic gland substance, watery extracts or saline extracts of the thymus, observers are almost unanimous in reporting it as a decrease. Reference is made to Ott and Scott (5), Miller and Miller (8), Schäfer (18), Popper (19), Basch (20) and Lucien and Parisoot (21). Popielski (13) states that an acidulated watery extract of thymus

caused a rise of blood pressure.

Reference to our previous paper (1) on this subject will show that we found the amount of bile secreted after the administration of thymic substance to be decreased. This effect was still in evidence in three out of four experiments in which a count was made for a second period of twenty minutes after the injection.

Thyroid. Substance of the thyroid gland was injected into nine dogs. In two of the experiments, numbers 6 and 33, no record of blood pressure was obtained. The other seven all show an initial rise in pressure, a sharp fall, a second gradual rise and a fall to normal. Pressure during the second twenty-minute period following the injection was practically the same as in the period preceding the injection. Average figures for these experiments follow: Initial pressure 105.8 mm.; first maximum 119.4 mm., 19 sec. from beginning; minimum 86.5 mm., 43.4 sec. from beginning; second maximum 117.7 mm., 191.4 sec. from beginning, and pressure at end of period 110.2 mm.

Other observers have usually found a fall in blood pressure to result from the administration of thyroid extract or thyroid gland substance. Oliver and Schäfer (17), Haskovec (22), Georgiewsky (23), Guinard and Martin (24), Fenyvessy (25), v. Cyon and Oswald (26), v. Fürth and Schwarz (27), all report a fall in pressure. Ott and Scott (5) used iodothyrin and obtained a marked fall with subsequent gradual

rise above normal. Schäfer (18) observed a considerable fall when using thyroid extract. Vincent (9) usually noted a fall but occasionally a rise of pressure. Levy (30) records no appreciable alteration in blood pressure after the intravenous injection of Kendall's crystalline thyroid iodine compound. A rise in pressure is reported by Popielski (13), Heinatz (28) and Livon (29).

So far as bile formation is concerned thyroid substance was without constant effect. Experiments 6, 28, 40 and 51 show an increase averaging 82.29 per cent. in the first period after the injection. Experiments 12, 17, 33, 37 and 58 show a decrease averaging 33.85 per cent. for the same period. Nevertheless, in spite of the wide variations in amount of bile secreted, the blood pressure ran a very similar course in all of these experiments.

Discussion

While the foregoing experiments are too few in number to permit definite conclusions to be drawn one thing seems certain, viz., that there is no constant relation between blood pressure and the amount of bile secreted. Adrenalin, it is true, consistently raised blood pressure and lowered bile formation; secretin, on the other hand, where it caused a change in blood pressure, produced a lower pressure and a great increase in the flow of bile. It might be urged that thyroid gland substance owes any action it exerts

upon blood pressure and bile formation to the intervention of the adrenals and this cannot be entirely controverted by our experiments. That thyroid substance increases the output of adrenalin has been shown by Büchner (31), Rudinger, Falta and Eppinger (32) and Gley and Quinquaud (33). In our experiments, however, there was no constant relationship between blood pressure and bile production after the administration of thyroid gland substance. We did not find bile production regularly decreased when blood pressure rose or vice versa. With others of the gland substances employed the blood pressure might be lowered and bile production decreased at the same time. The most striking example of this is in the series with pancreatic substance Intravenous administration of the substance of the pancreas caused lowering of the blood pressure and lessening of the output of bile. To a lesser extent thymic substance acted in the same manner. If we place in contrast with this the effect of secretin it would seem that we are not justified in concluding that the effect on bile formation is due to the alteration in blood pressure.

With the other gland substances employed, viz., mammary, orchic, ovarian and splenic, the results were inconstant. Orchic substance, for instance, caused a rise of blood pressure in some of our experiments and a drop in others while the production of bile was definitely lowered. After the administration of substance of the ovary blood pressure showed oscillations,

or waves of higher and lower pressure. The pressure at first rose above the original level, then fell below the initial, rose again and returned to the original. Biliary secretion was lowered in every case and an examination of the individual records of these experiments does not show any synchronism between changes in blood pressure and the rate at which the bile was secreted.

Conclusions

1. As a result of the experiments set forth in this paper we feel inclined to believe that some at least of the endocrine organs exert a specific influence on the secretory activity of the hepatic cells leading to the production of bile.

2. The output of bile in the dog is increased by the administration of secretin.

3. The output of bile in the dog is decreased by the administration of adrenalin, and by mammary, orchic, ovarian, pancreatic and thymic gland substances.

4. The amount of bile secreted is not affected in a constant or definite manner by the substance of the spleen and thyroid gland.

5. Blood pressure is raised by adrenalin.

6. Blood pressure is lowered by pancreatic substance and the secretin preparation employed.

7. A fall of blood pressure, ordinarily preceded by a slight rise, is caused by orchic and mammary gland substances.

8. Oscillations of blood pressure are

caused by ovarian and thyroid gland substances.

9. Blood pressure is not usually affected by splenic and thymic gland substances.

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VISCOSITY AND OSMOTIC PRESSURE IN RELATION TO ARTERIAL BLOOD PR

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The blood normally exists in the blood vessels under pressure pressure varies in the different parts of the circulatory system with the phase of the heart's action, i.e., whether the heart is ed or relaxed. The pressure in the arteries is high and positive, capillaries low and positive, in the small veins positive, but as heart is approached becomes negative. The pressure in the arteries time of the heart's contraction is called the systolic pressure a mally ranges from 110 mm. to 130 mm. of mercury; when the heart re the pressure is called diastolic and normally ranges from 65 mm. of mercury; the difference between the systolic pressure and the pressure is the pulse pressure. Blood pressure is maintained by th of the heart beat, the peripheral resistance, and the quantity of It is with the last named factor that we have now to deal and as w ered with our inquiry we shall see the important part played by vi and osmotic pressure in securing to the organism a sufficient quan of circulating fluid.

Let us consider first the mechanism by means of which a cons blood volume is normally maintained, for, with widely varying flu there must be frequently a tendency toward disturbance of the equ and toward an alteration in the volume of the blood. In 1913 Boye found that, in normal rabbits, the original volume of the blood w tored in a short and fairly constant interval after intravenous i of Ringer's solution (Sodium chloride 0.7%, potassium chloride 0.

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The blood normally exists in the blood vessels under pressure. This pressure varies in the different parts of the circulatory system and also with the phase of the heart's action, i.e., whether the heart is contracted or relaxed. The pressure in the arteries is high and positive, in the capillaries low and positive, in the small veins positive, but as the heart is approached becomes negative. The pressure in the arteries at the time of the heart's contraction is called the systolic pressure and normally ranges from 110 mm. to 130 mm. of mercury; when the heart relaxes the pressure is called diastolic and normally ranges from 65 mm. to 90 mm. of mercury; the difference between the systolic pressure and the diastolic pressure is the pulse pressure. Blood pressure is maintained by the force of the heart beat, the peripheral resistance, and the quantity of blood. It is with the last named factor that we have now to deal and as we proceed with our inquiry we shall see the important part played by viscosity and osmotic pressure in securing to the organism a sufficient quantity of circulating fluid.

Let us consider first the mechanism by means of which a constant blood volume is normally maintained, for, with widely varying fluid intake, there must be frequently a tendency toward disturbance of the equilibrium and toward an alteration in the volume of the blood. In 1913 Boycott found that, in normal rabbits, the original volume of the blood was restored in a short and fairly constant interval after intravenous injection of Ringer's solution (Sodium chloride 0.7%, potassium chloride 0.035%, calcium chloride 0.025%). In August, 1916, Bogert, Underhill, and Mendel published the results of several series of investigations upon the regulation of blood volume in normal and nephritic rabbits and dogs after the

injection of saline solutions, of saline-colloidal solutions, and of alkaline-saline solutions. Their conclusions are summed up as follows:

The regulation of the blood volume in normal animals is both rapid and efficient; for complete restoration of the original blood volume takes place within thirty minutes after the intravenous injection of a quantity of saline solution equal to the calculated blood volume of the animal.

The activity of the kidneys is not essential to this regulation of the blood volume, as it occurs even after ligation of these organs.

In conditions of nephritis inability to restore the blood volume to normal after injections of saline solution usually manifests itself.

The factor of species is probably of little importance in studies on this regulation of the blood volume since dogs and rabbits react alike when the conditions are identical.

Restoration of the blood volume to normal after intravenous injections of saline solutions is not primarily effected by the transfer of the excess of fluid from the blood vessels to the thoracic lymphatic system. The tissues act as a reservoir for this fluid.

The capacity of the tissues of rabbits to absorb fluid is approximately four times the normal blood volume of the animal.

Fluid injected in the form of colloidal solution may leave the circulation as readily as that in non-colloidal solution; but usually the regulation of the blood volume is less efficient after the injection of colloidal solutions.

The addition of alkali, up to 0.4% sodium carbonate, to the fluid injected has no apparent effect on the regulation of the blood volume in normal or in nephritic animals.

Thus far we have been discussing the question of the maintenance of a normal quantity of blood where there has been an increase in the amount of fluid within the vessels, all of which has a bearing on what is to

follow. During the winter of 1915-1916 my interest was aroused in the other side of the question, viz., a decrease in the amount of fluid in the blood vessels. It is common knowledge that a very abundant loss of blood causes death. The blood has for its functions to insure the physical conditions of the life of the cells as well as to maintain an excitability of the nerve cells which govern respiration and circulation. Every considerable loss of blood disorders cell life in the organism, tending to cause death. Necrosis very soon manifests itself when a member has by some procedure been deprived of its normal supply of blood. When the loss of blood has been from the whole system, and not confined to any member, a general death precedes the local death of the cells, because the oxygen not going to the cardiac and respiratory centers the functions of the heart and lungs are arrested. The principal symptoms of great loss of this vital fluid are general paleness and lower temperature of the cutaneous surface, oppression, breathlessness, stoppage of the secretions, and general convulsions.

Periodically in medical and surgical practice we are brought face to face with a series of signs and symptoms that are in essence the expression of an abnormally low blood pressure. Not alone is the list of pathologic states in which a low blood pressure is observed very long, but the explanations given by different authors as to why the low blood pressure exists in any given state are very different. From a therapeutic point of view, however, this ground is held in common by all: that a saving of life is intimately associated with, or rendered possible, only by our success in raising the blood pressure and keeping it up until such time as the patient himself succeeds in overcoming the conditions which are responsible for the low pressure. Simple as it would seem to attain this end its accomplishment practically is still a matter of debate. The problem involved is perhaps best presented if we consider the effects of simple haemorrhage. If by accident or otherwise one of the

larger vessels in man or a laboratory animal is opened we observe following each other in rapid succession all these alarming signs which reach their climax in death. When now we try to say why this occurs it is quickly brought home to us that the most serious mischief done by the haemorrhage does not reside in a great loss of red blood corpuscles or in a loss of certain of the chemical constituents found in the blood, as the haemoglobin or certain salts, but in a diminution in the volume of the circulating blood. After haemorrhage the blood pressure is low on account of deficieney of blood in circulation, so that the output of the heart is decreased and is insufficient to keep up a due supply in the arteries to take the place of that flowing through the capillaries. Now, while it is obvious that constriction of the arterioles would raise the pressure in such cases, by diminishing the rate of outflow through the capillaries, the result would be to decrease the supply of blood to all organs whose arterioles are affected, so that no real gain would be obtained. In such cases what is needed is to increase the volume of blood without constricting arterioles.

Transfusion is a process by which blood is conveyed from one animal to the vascular system of another. It was shortly after Harvey's discovery of the circulation of the blood that this operation was first practised by Denis, of Paris. He transfused with success the blood of a lamb into that of a man. It was believed that a great panacea had been discovered whereby not only blood lost by haemorrhage could be replaced, but a cure effected for many diseases and infirmities. Subsequent attempts proved such miserable failures that the operation was abandoned and even proscribed by law. More than a century later it was revived, but only after much experimentation on the lower animals. The knowledge gained thereby was to the effect that, for the operation to be at all successful, blood of the same species of animal should be used as the one on which it was performed. It was only after the establishment of this rule that it appeared possible to determine the value of transfusion and to make application

of it, with some degree of safety, to man.

In practice there are two kinds of transfusion: blood with fibrin, and blood without fibrin. In the first method the great danger is that coagulation will be caused in the vessels of the person receiving the blood. Another danger is the possibility of the entrance of air to the circulation of the recipient, which will be pumped into the blood vessels of the lungs, arrest the pulmonary circulation and cause death. In using defibrinated blood there is still the danger of intravascular clotting and also of the introduction of bacteria.

Because of the difficulties and dangers attending transfusion various artificial solutions have been manufactured, and the one most generally employed is warm, sterilized, physiological salt solution (sodium chloride 0.75%). This is injected either subsutaneously or into a vein. Ringer's solution, mentioned in connection with Boycott's experiments, is also used frequently.

I was able to show in detail the effect on arterial blood pressure of the withdrawal from the circulation of various amounts of blood and the result of intravenous injection of normal saline solution in amounts less than, equal to, and greater than, the quantity of blood lost.

In general it may be stated that removal from the circulation of 5 cc. of blood per kilogram of body weight is without influence on the blood pressure. Upon the withdrawal of the second portion of 5 cc. per kilogram blood pressure begins to fall and there is a fairly constant fall of blood pressure with the removal of each successive portion until 20 cc. or 25 cc. per kilogram have been withdrawn. The fall of pressure with the loss of each 5 cc. of blood per kilogram averages 6 mm. of mercury. After 20 cc. or 25 cc. per kilogram have been removed the loss of more blood causes a more rapid fall in pressure. At this point we find that each 5 cc, of blood lost per kilogram causes an average fall in blood pressure of 10 mm. and when 35 cc. to 40 cc. per kilogram has been

lost the animal is in a condition of shock with a blood pressure varying in different animals from 22 mm. to 35 mm. of mercury.

If normal saline solution be injected during the first stage of haemorrhage, that is while the blood pressure is falling slowly, there is a rapid and permanent return to normal. This is exemplified by the following experiment:

Rabbit; blood pressure before haemorrhage 84 mm.

Blood withdrawn	5	cc.	per	kilo;	blood	pressure	80	"
"	"	10	"	"	"	"	"	71	"
"	"	15	"	"	"	"	"	66	"
"	"	20	"	"	"	"	"	59	"
Normal saline	20	"	"	"	"	"	82	"

If the injection of normal saline solution be made during the second stage of haemorrhage, that is during the period of rapid fall of blood pressure, the permanent return of pressure to normal can be accomplished, but the response is much slower than in the first stage. Immediately following the saline infusion the pressure rises 20 mm. or even 30 mm. In one case it rose 38 mm. After the initial rise the return to normal is slow and requires from twenty-four hours to forty-eight hours.

If the injection of saline solution be deferred until the third stage of haemorrhage, i. e., until collapse has occurred, the possibility of bringing about a permanent restoration of blood pressure is remote. The first effect of the saline injection is a rise of blood pressure, this rise usually being about 10 mm., although in one case it was 20 mm. Repeated injections of large amounts of saline solution are without further effect under these conditions, with very infrequent exceptions, and fail entirely to [illegible].

From these observations we draw the conclusion that so long as the haemorrhage has not been great enough to reduce blood pressure to the "shock level" gratifying results may be hoped for from the intravenous administration of normal salt solution. When the blood pressure has

reached the level of shock, 30 mm. to 50 mm., restoration of blood pressure and maintenance of the vital functions of the organism are a possibility, but can not be expected with any certainty.

As will be seen presently, there are two separate phenomena requiring explanation. Why is saline solution relatively ineffective in restoring pressure? And, secondly, why does the pressure actually produced fall again more or less rapidly to a value very little higher than before the injection.

In regard to the former problem, we know that the cardiac output being supposed constant, the height of the arterial pressure depends on the resistance in the peripheral arterioles and that this resistance is entirely due to the internal friction or viscosity of the blood. The rate of flow is inversely proportional to the viscosity and directly proportional to the driving pressure, by Poiseuille's law. This law has been shown by Du Bois-Reymond, Brodie, and Müller to apply to the circulation, contrary to the objections of Heubner and others. The output of the heart being constant, by hypothesis, the rate of flow through the blood vessels must also be constant, and therefore if the viscosity of the blood decreases, the driving pressure must decrease also. Otherwise, the current through the capillaries would be larger than that supplied by the heart. In other words, the arterial pressure must fall.

Now, the viscosity of blood is considerably higher than that of water or of dilute saline solution. In the cats used in the experiments of Bayliss, from whom I shall quote largely from now on, it was usually about three times that of water, but in one case it was only 2.8 times and in another it was as high as four times. The viscosity of Ringer's solution, on the other hand, is practically the same as that of water. It follows that, if part of the blood is replaced by such a saline solution, the resulting viscosity is correspondingly reduced, and, other things equal, the arterial pressure must decrease. Thus, in one experiment,

the viscosity was reduced to 1.6 times that of water by replacing half of the blood by Ringer's solution. In another case it was reduced from 2.2 times to 1.8 times by the replacement of 47 per cent of the calculated blood volume by the saline solution. In one experiment several samples of blood of 45 cc. each were removed and replaced by saline in series, so that the viscosity decreased each time. The height of the arterial pressure decreased with the decrease in viscosity and in practically the same proportion.

It is evident that the diminution of viscosity is a sufficient explanation of the inefficiency of saline solutions, so far as the immediate effect is concerned. If, therefore, the viscosity of Ringer's solution could be raised by the addition of some innocuous substance a much better result would be obtained. In accordance with this thought Bayliss tried a number of substances.

Soluble starch has the disadvantage of not having sufficient viscosity, except in concentrated solutions. It does not give very homogeneous solutions and alters by keeping, even in the cold. The solution becomes acid by separation of phosphoric acid so that neutralisation is necessary each time that it is used. It has also the objection of a very small osmotic pressure.

Amylopectin has a high viscosity but an insignificant osmotic pressure.

Agar requires too high a temperature to melt the jelly and is practically devoid of osmotic pressure.

Gum acacia in 7 per cent solution has a viscosity about equal to that of blood. The commercial preparation has too high a per centage of calcium. This can be removed in sufficient quantity by the addition of deci-normal phosphoric acid and neutralizing with sodium hydroxide. To complete the solution the correct amount of potassium chloride is added.

Gelatin is very convenient in many ways as solutions are quickly made. If the maximum viscosity is required a temperature above 40 C. should not be employed in making the elution. If heated to 100 C., as Moore and Roaf showed, the osmotic pressure rises. The decrease of viscosity on heating is a disadvantage for clinical use since sterilisation is indispensable, owing to the usual presence of micro-organisms.

In experimental test it was found that injection of Ringer's solution containing one or more of these substances in sufficient quantity to raise the viscosity to that of blood, even when injected only in amount equal to that of the blood lost brought back the blood pressure to its original height, and sometimes temporarily above that height. The explanation of this latter fact will be seen immediately.

A cat with a blood pressure of 110 mm. of mercury had about half of the calculated amount of its blood removed. The pressure fell to 40 mm. It was brought back at once by the injection of an equal volume of Ringer's solution containing gum in sufficient quantity to raise its viscosity to 3.1 times that of water. In the course of a few minutes the pressure rose further to 145 mm. It soon commenced to fall slowly, but was still at its initial value of 110 mm. at the end of 43 minutes. It had fallen to only 102 mm. in one hour and to 98 mm. in 75 minutes. Similar results were obtained with gelatin.

We see that by raising the viscosity of the injected fluid to that of blood by the addition of gum or gelatin, the blood lost can be replaced by an equal volume of the solution, with a return to its original height. Furthermore, this height is maintained for an hour or so, and even then has fallen only to an unimportant degree. Pure Ringer's solution, as shown above, is very inefficient in maintaining the blood pressure even at the height to which it at first raises it. Why do gum and gelatin behave differently in this respect? It is clear that viscosity alone

is not a sufficient explanation. The fact that gelatin solutions caused a more permanent rise of blood pressure than pure saline was noted by Hogan and Fischer, and that saline solutions containing 3 per cent of gelatin did not leave the blood vessels as rapidly as pure saline was recorded by Bogert, Underhill, and Mendel.

A partial explanation of these facts is given by Knowlton's experiments on the secretion of urine. Starling showed that if the osmotic pressure of the blood colloids, to which the membrane of the glomerulus is impermeable, be reduced by dilution of the blood diuresis results. This is the case when a pure saline solution is injected. Knowlton shewed that by the addition of a colloid which has an osmotic pressure, such as gelatin, the effect of the dilution is greatly decreased. Further, if a colloid which has no perceptible osmotic pressure, such as soluble starch, be added instead of gelatin, the diuresis is as great as with saline. The loss of the injected fluid by renal excretion does not, however, explain the phenomenon of the fall of blood pressure. It was sometimes found in the experiments of Bayliss that very little urine was produced after the saline injection. But what concerns us is that, although there may be no increased loss of fluid by renal excretion, yet the arterial pressure falls rapidly after saline injections. The additional factor is,no doubt, passage of fluid into the tissues. Bogert, Underhill and Mendel have shown that saline solutions pass into the tissues rapidly and that the kidney is not necessary for the removal of excess of fluid from the circulation after intravenous injections into the normal animal. We have also seen that the blood pressure remains high for a long time after the injection of gum or gelatin, but falls after starch solutions. Clearly, then, gum and gelatin differ from starch in the possession of osmotic pressure.

Starling has emphasized the importance of the osmotic pressures of

the protein content of blood and tissue fluids in the passage of water from one to the other. The protein content of the blood plasma is higher than that of the tissue lymph, so that there is a continual attraction of water from the tissues to the blood. This is, however, normally balanced by filtration in the other direction, which occurs where the pressure in the blood vessels exceeds the difference between the osmotic pressure of their contents and that of the tissue fluids. If, on the other hand, the blood is diluted, so that the osmotic pressure of its colloids is lowered, an internal pressure of the same height as before will cause greater filtration, and, at the same time, the difference between the osmotic pressure of the blood and that of the tissue fluid being less, there is a decreased osmotic attraction of water by the blood from the tissues. The two causes combine to produce oedema. The colloid added to increase the viscosity of an intravenous injection must therefore possess an osmotic pressure equal to that of the colloids of the blood.

The question is, then, Are we to take as the required colloidal osmotic pressure of our ideal injection fluid that against water or against Ringer's solution? If the wall of the blood vessels consists of a membrane permeable to crystalloids, impermeable or nearly so to colloids, it will behave as the parchment paper membrane of our osmometer and we must take the osmotic pressures as measured against Ringer's solution as those which come into play. We require a solution of a colloid which gives under these conditions an osmotic pressure of about 40 mm. of mercury. This is given by a 7 per cent solution of gum or a 6 per cent solution of gelatin. The viscosity of such solutions is only very little higher than that of blood. If stronger solutions are used water is attracted from the tissues and the blood is diluted.

As already pointed out, with equal cardiac output the rate of blood flow through the organs remains the same, although the arterial pressure

may be higher , if this rise of arterial pressure is due to increased peripheral resistance from rise of viscosity. It might be thought that increased viscosity is not desirable since the work of the heart is increased thereby. In practice, however, the output of the heart falls with a low blood pressure, partly owing to insufficient inflow from the veins, partly owing to the heart muscle suffering from deficient supply of oxygen.

Summary.

When the arterial pressure is low from loss of blood it can not be brought back, except to a certain degree, by the injection of saline solution in volume equal to that of the blood lost. But if the viscosity of such solutions is raised to that of the blood a return to normal height is possible.

The effect of saline injections is also much less lasting than that of solutions containing gum or gelatin. The difference in this case is due to the osmotic pressure of the colloids by which loss of water by the kidneys and to the tissues is prevented.

It is desirable, therefore, to increase both the viscosity and the colloidal osmotic pressure of solutions used for intravenous injection after loss of blood. This can be done effectively by the addition of 6 per cent. gelatin or 7 per cent. gum acacia to Ringer's solution.

I must again express my indebtedness to Professor W. M. Bayliss for a large part of this paper.

(Read) April 8th
a review, not original work.

Read before the Medical Literature Club
of Philadelphia, Pa., in 1915. (I have no
record of the exact date).

REVIEW OF THE RECENT WORK ON THE FUNCTIONS OF THE PITUITARY BODY.

Ever since the important discovery made by P.Marie, in 1886, that the disease known as acromegaly is associated with pathological changes in the pituitary body, this gland has had a special interest both for the clinician and the physiologist. Histologically and embryologically it consists essentially of two parts, or lobes, the anterior and posterior. The anterior lobe, or pars anterior, is derived from an epithelial outgrowth from Rathke's pouch. The posterior lobe includes the pars intermedia, derived from the glandular or anterior portion, and the pars posterior, derived from the wall of the third ventricle of the brain. The pituitary body yields two secretions that of the anterior lobe finds its way into the blood vessels, and is depressor--it lowers blood pressure; that of the posterior lobe is formed in the pars intermedia and finds its way through the pars posterior into the third ventricle, where it mingles with the cerebro-spinal fluid. The functions of this secretion are varied.

After the discovery of Marie the next important contribution to our knowledge of the functions of this gland was that of Oliver and Schafer, in 1894, They found that intravenous injections of saline extracts of the entire organ produced a marked rise in blood pressure, not so great as in the case of adrenalin but more prolonged. This action is peripheral and is due mainly to constriction of the arterioles. Howell showed that this pressor effect is obtained only from extracts of the posterior lobe. Also the heart is stimulated to beat more powerfully and more slowly even after division of the vagi, and unlike the active principle of the adrenals the pressor substance of the pituitary acts directly on the muscle of the heart and blood vessels and not through the nervous system. It appears to have a stimulating effect on involuntary muscle in general, as shown by the experiments of Frohlich, von Frankl-Hochwart, Cramer, and others. Because of this action it has been used in obstetric practice in cases of post-partum haemorrhage and to promote uterine con-

traction.

The diuretic action of extract of the posterior lobe was first demonstrated by Magnus and Schafer, in 1906, and later by Schafer and Herring. These investigators observed that while the general effect of intravenous injection on the systemic circulation was vaso-constriction, the local effect on the renal vessels was usually dilatation, and that this was accompanied by an increased secretion of urine. That the diuresis was not due to the increased flow of blood through the kidney, or not entirely due to this, was shown by the fact that in several experiments where no renal vaso-dilatation was observed there was still a distinct increase in the flow of urine, indicating a direct action on the secretory epithelium of the kidney.

In 1910 Ott and Scott found that infundibulin, the active principle of the posterior lobe, injected intravenously produced a marked increase in the rate of secretion of the mammary gland of the goat. A few months later Schafer and Mackenzie where able to confirm these findings by experimenting with lactating cats and dogs. In about 20 seconds after injection the mammary gland responds by a greatly increased flow of milk. The effect passes off after 3 or 4 minutes and a repeat dose given within one-half hour produces a much smaller quantity of milk than the first dose. In both these respects, short duration of flow and diminished response after each injection, the effect differs from that of the same extract on urinary secretion. Mackenzie found also that the galactogogue substance is present in the pituitary body not only of lactating females but also of non-lactating females and of males. It is not even specific to mammals since it is present in the pituitary of birds.

Mackenzie made one experiment on a human subject, a hospital patient, who was suffering from a unilateral mammary abscess, the healthy breast being observed. The breast was emptied by a suction apparatus, 60cc. of milk being obtained. Infundibular extract was then administered subcutaneously and an hour later the breast was again aspirated when 100 c.c. were obtained. Although not conclusive this experiment supported the results obtained from the cat.

Without going into the details of the experiments of Gavin, who undertook to determine whether from the commercial point of view the amount of milk per diem or its quality is influenced by extracts of the pituitary body, it suffices to say that he concludes "that under conditions of ordinary farm practice no commercial benefit arises from the administration to dairy cows of these extracts." These results were published in July, 1912. In October of the same year Schafer published the results of an experiment carried out on a lady of twenty-eight years, who was nursing her second baby and at five months was beginning to yield less milk than the baby required. Four injections into the triceps were made at intervals of two or three days, the dose varying from 1 c.c. to 1.5 c.c. of pituitary extract, each 1 c.c. representing 0.2 grams of fresh posterior lobe. The results, given in the patient's own words, were as follows: "The first injection produced no apparent effect; on each of three subsequent injections there was an immediate effect, I could feel the milk coming in with a tingling sensation, but so far as I can judge no lasting effect. I judge this from the fact that though there was more milk than usual for the baby for the meal following the injection, I had to wait a long time before I could feed him again, and in spite of the injections my milk is gradually getting less in amount. It had, however, begun to diminish very decidedly before the injections were started". That there was an actual increase following the administration of the extract is shown in one of the experiments where the milk was pumped from the breast during five minutes a quarter of an hour before injection and again during five minutes half an hour after injection. In the first five minute period 9 c.c. of milk was yielded and in the second 32 c.c.

The next to investigate this matter was Hammond, working with Dr. F. H. A. Marshall of Cambridge, England. He used three goats in various stages of lactation. The usual dose was 1 c.c. of the extract of the posterior lobe of the pituitary injected subcutaneously, and a careful analysis of the milk yielded before and after injection was made. His conclusion is that "the injection of the

extract has an immediate action on the milk secretion,but the effect soon passes off so that the daily yield is only slightly raised.The milk obtained as a result of injection is normal in composition except for a higher percentage of fat;in the following milkings,however,there is a drop in the percentage of fat although that of the other constituents remains normal."

Sutherland Simpson and R.L.Hill have recently investigated the effect of pituitary extract on the secretion of milk in the goat and the cow.They used larger doses than had been employed before and gave the extract intravenously.Their conclusions are that injection of the whole gland or of the posterior lobe alone leads to an immediate secretion of milk very rich in fat.The effect,however,quickly passes off.There is a corresponding diminution in the yield of milk at the next milking period,and to some extent in the percentage of fat,so that for the 24 hours there is practically no increase in the total quantity of milk or of fat obtained.

The bearing of these observations on the normal functions of the pituitary body is interesting but it must be remembered that great caution has to be exercised in interpreting the results obtained from the injection of any glandular extract.Although several active substances may be present in the pituitary extract it does not necessarily follow that these same substances are being continuously or intermittently produced by the gland in the living body and passed into the circulation.Before we can be certain that these substances are formed in the living organ we must find indications of their presence in the blood or lymph as it leaves the gland,or in the cerebro-spinal fluid.Cushing and Goetsch claim that the active principles are to be found in the cerebro-spinal fluid,for when this is slightly concentrated and injected intravenously effects similar to those which follow injection of the extract are obtained.This has been questioned,however, by Carlson and Martin.

There also arises the question as to whether each of the actions known to be produced by injection of the extract is due to a distinct and separate

substance or are they all brought about by the same substance. Although an answer can not be given with certainty there is much evidence in favor of the first view. Cramer's observations tend to show that the substance which acts on the pupil is not identical with that which excites renal activity. Recent work by Herring indicates that the galactogogue also is a distinct substance, not identical with any of the other active principles, since he finds that the pituitary extract of the skate has no effect on blood pressure, kidney volume or urinary secretion, but does excite the mammary gland.

Removal of the entire gland causes death in three or four days. The same symptoms follow removal of the anterior lobe alone, and develop just as rapidly as when the whole gland is taken away. Loss of the posterior lobe alone does not appear to have any disturbing effects unless it be excessive sexual activity.

Partial removal of the anterior lobe gives rise to symptoms resembling those present in Frohlich's disease; viz., adiposity, sexual infantilism, mental dulness, and subnormal temperature.

According to the view originally put forward by Marie diminished pituitary function is the primary cause of acromegaly, but at the present time just the opposite view is held by most authorities. As in the case of the thyroid there are characteristic symptoms associated with hyperactivity and with hypoactivity of the gland. If hyperactivity occurs early in life giantism results, if later, acromegaly. Similarly with regard to hypoactivity the type differs according to the age at which the condition appears. Adiposity is a common feature, with genital hypoplasia, mental dulness, and if the disease begins in childhood skeletal underdevelopment. In all these conditions it is believed to be the anterior lobe which is primarily affected.

The relationships which may exist between the pituitary and the other glands producing an internal secretion are still to a large extent unknown. Attempts have been made (Vienna school) to construct schemes of interrelationship of all the ductless glands with each other. The idea of a vicarious action

between the thyroid and pituitary was first suggested by Rogowitsch.He found that following thyroidectomy in the rabbit there was hypertrophy of the pituitary body.This has been confirmed by many(Herring and Hegener).The interrelation between the glands of reproduction and the hypophysis appears also to be well established.One of the most constant symptoms of hypopituitarism, clinical and experimental,is hypoplasia of the reproductive glands with suppression of the secondary sexual characters.The converse of this is shown by some experiments of Cushing and Goetsch,where they fed dried extract to young rats. They conclude that pituitary extract,and particularly that of the anterior lobe,has a markedly stimulating effect upon the growth and development of the reproductive glands in both sexes.

In conclusion,it must be admitted that our knowledge of the functions of the pituitary body is still very incomplete,but important facts are steadily being accumulated.Practically all we know about this gland has come to us within the last thirty years,or since Marie's discovery in 1886.

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Read April 11.

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Read before McGill Chemical Society,
February 15, 1918.

THE REGULATION OF RESPIRATION

Mr. Chairman, Ladies and Gentlemen:

In this paper it has been my endeavor to present for your consideration the latest work that hasbeen done on the subject of chemical factors in the blood in relation to the activity of the respiratory centre. Since the efferent nerves supplying the respiratory muscles leave the cerebral axis over a long region it is reasonable to suppose there is a centre which regulates and controls the activities of these various motor centres. Also as there are inspiratory and expiratory systems of muscles it is probable that there are inspiratory and expiratory parts of the governing centre. This centre is located in the medulla close to the centres of the vagus nerves,and is modified in its activity by extraneous impulses. These impulses may be through the bloodor through afferent nerves.

As the aim of respiration is to supply oxygen to and remove carbon dioxide from the organism it is not surprising that some of the earliest views on the cause of respiration were founded on the presence of these gases in the blood. The earliest investigators put down the active substance as carbon dioxide in excess in the blood.(Marshall Hall, Traube), but this was subsequently replaced in the minds of scientific men by the idea of lack of oxygen (Rosenthal, Pflueger). It may be considered as definitely proved that in normal respiration lack of oxygen plays no part. The belief that carbon dioxide is the substance which normally excites respiration was confirmed and extended by Haldane and Priestly, who showed that respiration is so regulated as to keep the alveolar and blood tension of carbon dioxide practically constant for the same individual.

A similar conclusion as to the use of carbon dioxide in respiration has been reached by Zuntz.

It must not be concluded that the chemical composition of the blood is the sole factor in the regulation of respiration for it has long been known that impulses reaching the centre along afferent nerves modify the respiratory movements. From the work of many we know that the only nerves which have a continuous effect on the centre are the vagi and the work of Hering and Breuer showed that these impulses originated in the lungs themselves. The vagi, in reference to the movements of respiration, must be regarded in the same light as the sensory nerves of muscle. Without the vagi the muscular movements are excessive, and thus resemble the movements of an ataxic limb.

It is generally accepted at the present time that the hydrogen ion concentration of the blood is alone concerned in the chemical regulation of respiration. Haldane and his co-workers laid the foundations for this conception of the respiratory function but Winterstein was apparently the first to present the facts in the form of a concrete hypothesis. This hypothesis has received fundamental support in the work of Hasselbalch, Barcroft, and others, and has been successfully employed as a basis for the treatment of disease and for the explanation of numerous physiological processes.

A few months ago Scott published the results of a number of experiments on the effect of the accumulation of carbon dioxide on the tidal air and on the H-ion concentration of the arterial blood. These experiments were performed in an attempt to produce a definite change in the H-ion concentration of the arterial blood due solely to carbon dioxide and to study the coincident response of the respiratory centre and the total carbonate content of the arterial

blood in an animal breathing gradually increasing percentages of carbon dioxide.

Hasselbalch and Lundsgaard have demonstrated that the addition of CO_2 to blood in vitro will raise its C_H. Conversely the removal of carbon dioxide from the blood causes a fall in C_H. Milroy, working with etherized cats and dogs found that a definite fall in the H-ion concentration of arterial blood resulted from forced pulmonary ventilation, and that in two experiments in which the animals breathed gas mixtures rich in carbon dioxide he obtained a rise in the H-ion concentration of the blood. With the exception of a few experiments reported by Hasselbalch and Lundsgaard there are very few data on the quantitative response of the respiratory centre to carbon dioxide together with a determination of the C_H of the blood. Many attempts have been made by clinicians to prove that certain types of dyspnoea represent a condition of true carbon dioxide acidosis; that is, are primarily due to retained carbonic acid rather than to other acids. These attempts, however, have been attended with very little success. Peters in a recent paper has discussed the difficulties of determining the existence of carbon dioxide acidosis as the cause of cardiac dyspnoea.

Although it is practically impossible to duplicate in animals the pathological conditions responsible for certain types of clinical dyspnoea, nevertheless one can produce an accumulation of carbon dioxide and study the effect of the retained carbonic acid on the respiratory centre, the H-ion concentration and the total carbonate content of the arterial blood. Given a respiratory centre with normal sensitivity it matters little what may cause an accumulation of carbon dioxide; other things being equal, the effect on the centre and on the H-ion concentration of the blood will be the same. In the

experiments of Scott decerebrate cats were used as the experience of other workers in this field has been that they were unable to find any anaesthetic which did not depress the respiratory centre if given in sufficient dosage to prevent struggling. In some experiments with urethanized cats the respiration was apparently normal when breathing atmospheric air but when the animals were made to breathe increasing quantities of carbon dioxide in a closed system the response of the respiratory centre was quite unlike that of a decerebrte cat under the same conditions. The latter responded to gradually increasing percentages of carbon dioxide by a progressive increase in both rate and depth of respiration whereas the urethanized cat responded by an increase in depth only. The total increase in the tidal air for a given percentage of carbon dioxide was also different in the two cases. It is noted that when the decerebrate cat was breathing an atmosphere of 5% carbon dioxide there was an increase amounting to 414% in the tidal air per minute. Under the same conditions the urethanized cat had increased pulmonary ventilation by only 214%. That anaesthetics depress the respiratory centre is evidenced by the work of Cushny and Lieb. It is evident from these observations that even small doses of urethane so depress the respiratory centre that it will tolerate a much higher percentage of carbon dioxide than will a normal centre,(Michaelis, Davidoff, Newburgh, Means, Porter). Hence the sensitivity of the respiratory centre is a very important factor in maintaining at its normal level the molecular ratio $\frac{H_2CO_3}{NaHCO_3}$ and consequently the H-ion concentration of the blood. In order to retain this normal sensitivity the method of decerebration devised in Sherrington's laboratory is employed.

With a gradually increasing percentage of carbon dioxide in the

inspired air a point is reached where, in spite of the accelerated respiration, sufficient carbonic acid accumulates in the blood to produce a detectable elevation in the H-ion concentration. Accompanying this increase in carbonic acid there is a very considerable elevation in the bicarbonate content above normal. During the preliminary period while the animal is respiring atmospheric air the molecular ratio, carbonic acid to sodium bicarbonate, of the arterial blood is 1.4 :28.9. At the end of the rebreathing period, when the carbon dioxide in the inspired air has increased to 6.45%, the ratio is3.8:49.6. Although there is an absolute increase in the blood bicarbonate from 28.9 to 49.6 (in terms of volume per cent carbon dioxide), the ratio carbonic acid:sodium bicarbonate has increased from 1/20.6 to 1/13.

It was shown many years ago by Zuntz that the introduction of carbon dioxide into blood raises not only the carbonic acid but also the bicarbonate content. Any condition therefore which causes an abnormal retention of carbon dioxide in the organism must lead to disturbances in the chemical equilibrium in the blood in the direction indicated. Such conditions fall under four general heads. They may act singly or any combination of the four may be responsible:

1. Increase in general body metabolism; e. g., fevers, exercise.

2. Lowered sensitivity of the respiratory centre; e. g., narcosis, comatose states.

3. A high percentage of carbon dioxide in the inspired air.

4. A failure on the part of the organism to eliminate an adequate quantity of carbon dioxide; resulting from:

a. A poor mass movement of blood through the lungs, as in heart disease.

b. Some interference with the passage of carbon dioxide from

the venous blood to the alveolar air.

c. An impediment to the mechanics of respiration thereby causing an interference with the free ingress and egress of air.

The above data indicate that we are dealing with a condition of true carbon dioxide acidosis. When the animals inspired an atmosphere containing 5 to 6 per cent carbon dioxide the increased activity of the respiratory centre was inadequate to maintain the the molecular ratio carbonic acid : sodium carbonate at a normal level. The accumulated carbonic acid was to a large extent converted to sodium carbonate yet there was still a sufficient elevation in the ratio carbonic acid : sodium carbonate to produce a demonstrable elevation in the H-ion concentration of the blood. If we accept the hypothesis that the H-ion concentration of the blood is alone concerned in the chemical regulation of breathing, it follows that the first appreciable increase in the tidal air in the above experiments must have been due to an elevation in the H-ion concentration of such magnitude that, although it was sufficient to stimulate the respiratory centre, it could not be detected in the blood itself by any means at our disposal.

Much has been written in recent years on the subject of acidosis but there is still some disagreement over the definition of the term. No doubt much of the confusion is due to a failure to distinguish between acidosis and detectable acidosis. As defined by some authors, acidosis is a condition in which the bicarbonate in the blood is reduced below its normal level. Such a definition applies to the condition in which the acids responsible for the increased H-ion concentration are other than carbon dioxide, as in diabetes; but such a definition does not consider carbon dioxide acidosis in which, as shown, there is an increase in the bicarbonate

content of the arterial blood above normal.

That it is possible to have a depletion of blood bicarbonate without an actual increase in the H-ion concentration seems a debatable question. Koppel and Spiro have shown that the buffer value of a solution is directly proportional to the concentration of buffer substances in the solution. Accordingly, in so far as the blood bicarbonate is depleted below normal, the addition of the same amount of acid must produce a proportionally greater elevation in the H-ion concentration than in normal blood. In other words, the minute fluctuations in H-ion concentration that must occur under strictly normal conditions would be exaggerated, and in spite of the accelerated respiration would remain so until the bicarbonate was restored to its normal value. Assuming that even the normal quantity of acid products of metabolism is being added to the blood depleted in bicarbonate, it is evident that there must occur a greater elevation in H-ion concentration than would take place under the same conditions with normal blood. The respiratory centre is stimulated and lowers the carbonic acid thereby reducing to a more normal proportion the ratio carbonic acid : sodium bicarbonate, consequently the H-ion concentration of the blood is maintained within normal limits so far as our methods, at present available, are able to detect. Because an increase in H-ion concentration is not detectable is no evidence that it is not active.

Haldane, Douglass, Henderson and Schneider, from observations made on Pike's Peak found that the alveolar ventilation at that altitude was approximately 50 per cent greater than at sea level. This increased activity of the respiratory centre cannot be accounted for by the direct action of oxygen want, as shown by Boycott and Haldane, and we may conclude that the accelerated alveolar ventila-

tion at high altitudes is due to a slight increase in the H-ion concentration of the blood; an acid increment too small to be demonstrated by our most refined methods of measurement.

Reference to the experiments of Scott, (previously referred to,) shows that 2% carbon dioxide in the inspired air caused an average increase of 64 per cent in the tidal air per minute. Examination of the arterial blood at this stage revealed no demonstrable increase in the H-ion concentration but an appreciable increase in the total carbonate content. In this case, in so far as the accelerated respiration was adequate to maintain the H-ion concentration normal within detectable limits, we can call the condition one of compensated acidosis, but there is no reason to conclude that there was not an actual elevation in H-ion concentration responsible for the increased respiratory activity. When the inspired carbon dioxide has reached about 4% an increase in the H-ion concentration of the arterial blood becomes detectable by colorimetric methods.

It is possible that further light has been thrown on the problem of the chemical regulation of respiration by the experiments of Hooker, Wilson, and Connett published in May, 1917. Laqueur and Verzar believed they were able to show that carbonic acid acts as a specific respiratory stimulant; but the evidence which they offer is not convincing. Hooker and his co-workers perfused the mammalian medulla, using blood perfusates of which the H-ion concentration and carbon dioxide tension were known, and studied the effects produced by these two factors upon the activity of the respiratory centre. They have obtained evidence that carbonic acid exerts a specific influence upon the respiratory centre independent of its effect upon the H-ion concentration of the blood perfusate.

A number of preliminary experiments were performed which demonstrate the general nature of the response. Sodium bicarbonate and

sodium hydroxide depress respiratory activity; carbonic acid, hydrochloric acid, lactic acid and oxygen want increase respiratory activity. The effect upon the cardiac and vaso-motor centres appears to be of the same order as that upon the respiratory centre. That is to say, those substances which increase respiratory activity tend to increase the arterial blood pressure and heart rate, and those substances which depress respiratory activity tend to decrease the arterial pressure and heart rate. The response of the latter centres is what we should expect from our knowledge of the functional interaction of the respiratory and cardio-vascular centres. Nevertheless the action of these several substances on the cardio-vascular centres has not been discussed and the results are of interest.

Their experiments were directed primarily to a comparison of the respiratory response elicited by blood, the H-ion concentration of which was altered to the same degree by the addition of carbon dioxide and hydrochloric acid. To this end they used as a control blood which had been shaken to remove the excess of carbon dioxide and observed the physiological reaction produced by the substitution of bloods with higher H-ion concentration. In such a procedure one of the most important precautions to be observed is to guard against change in the irritability of the respiratory centre. The medullary centres undoubtedly lose in functional capacity in the course of perfusion and this rate of loss is not comparable in different experiments. It is evident, therefore, that the comparison of the response produced by two stimuli so closely alike as carbon dioxide and hydrochloric acid bloods is unsafe unless they are both tested in the same experiment; and, even then, the progressive loss of irritability may establish conditions such that the test of the

second specimen of blood is, for purposes of comparison, invalid. If, however, the perfusion of carbon dioxide blood produces the greater increase of respiratory activity when tested after as well as before hydrochloric acid, we may believe that the carbon dioxide blood is the more effective stimulus.

The defibrinated blood used as a control was agitated in air until its H-ion concentration had reached a minimum. One portion of this blood was placed in a flask and agitated while being exposed to an atmosphere of 5 per cent carbon dioxide in oxygen. The hydrogen ion concentration of this sample was determined by the indicator and electrical methods. A second portion was brought to the same reaction by treating with hydrochloric acid and shaking to remove the excess of carbon dioxide liberated. In this way two specimens of blood were prepared; one with a high tension of carbon dioxide and therefore containing a considerable quantity of free carbonic acid and a relatively high concentration of total carbonate; the other containing relatively less carbonic acid and total carbonate but with the same H-ion concentration.

The experiments bring out forcefully the difference in response to the two bloods. Carbonic acid blood when used before as well as after hydrochloric acid blood produces much the greater effect. As an example of the results obtained the following may be of interest:

Test blood	Reaction		Respiration						
	Con.	Ex.	Ampl.mm.		Rate		Amplitude X Rate		Percent change
			Bef.	Dur.	Bef.	Dur.	Bef.	Dur.	
CO_2 5%	7.6	7.31	3	35	69	87	207	3,045	1,366
HCl	7.6	7.31	45	40	48	75	2,160	3,000	39
CO_2 5%	7.6	7.3I	35	55	39	84	1,365	4,620	165

The greater efficacy of carbon dioxide is further indicated by the fact that in one experiment the hydrochloric acid blood ~~was~~ was perfused for two periods of eighteen and ten seconds respectively without eliciting a sharp reaction in either case, while the perfusion of carbon dioxide blood for two periods of four seconds each produced not only a much more decided reaction but one which exhibited itself much more promptly.

The experiments thus outlined appear to prove that blood with a comparatively high tension of carbon dioxide causes a greater stimulation of the respiratory centre than does blood with a lower tension of carbon dioxide but with the same H-ion concentration. The method of stimulation is unknown though several theoretical considerations are of interest. The reactions of the bloods were within physiological limits. As the bloods with higher H-ion concentration were still alkaline the diffusion of free acids other than carbonic may be considered negligible. (The variations in the concentration of the salts in the perfusates, incident to the alteration in the reaction of the blood do not have an appreciable inhibiting action on the respiratory centre, as other experiments have shown.) The cause for the smaller stimulation by the bloods to which hydrochloric acid was added,,and the excess of carbon dioxide shaken out, seems therefore to be due to the decreased concentration of carbon dioxide or carbonic acid. As the tendency for diffusion of carbon dioxide from the cells into the blood depends on the difference in the tension of carbon dioxide of the two systems, the higher the carbon dioxide content of the circulating blood, the slower the diffusion from the cells and the higher the concentration in the cells when a new equilibrium is established. The tension of carbon dioxide in the

respiratory centre would presumably, therefore, be higher in experments in which blood with a high tension of carbon dioxide was employed and, vice versa, low when blood with low carbon dioxide concentration was employed. It would seem that the hydrogen ion concentration of the two systems would likewise maintain an equilibrium. If this is true the H-ion concentration in the centre would be the same in both series of Hooker's experiments because the reaction of the two bloods was the same. The greater activity produced by the bloods containing the high tension of carbon dioxide would have to be explained as being due to some specific action of the carbon dioxide. Whether carbon dioxide as such stimulates the respiratory centre or whether variations in the carbon dioxide concentration alter the irritability of the respiratory centre can hardly be demonstrated. If we are to adopt an explanation for the results obtained in these experiments, the most satisfactory point of view would seem to be that the H-ion concentration of the environment of the respiratory centre is its effective stimulus but that the irritability of the centre to this stimulus may vary and be influenced by many factors. The normal irritability of the respiratory centre is doubtless the summation of a number of effects including those produced by carbonic acid, oxygen, and various ions, as well as changes in metabolic activity of whose nature we are still ignorant.

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PHYSIOLOGY AND AVIATION.

The physiologic effects of altitude on man have a three fold interest; one is a purely scientific interest in life under conditions of low barometric pressure, a second is due to the part that altitude plays in therapeutics (climatology), and a third is the result of the coming into prominence of aviation. The consensus of opinion held is that the physiologic effects noted at high altitudes are due to the lack of oxygen resulting from the lowered partial pressure of oxygen. Those disturbances brought on by change of altitude cause the so-called mountain sickness, the symptoms of which may be so mild as to be overlooked. Mankind differs greatly in the power of adjustment to changes of environment. Hence, it is found that mountain sickness befalls some individuals at a lower, others at a higher altitude, but it is certain that no one escapes the malady who proceeds beyond a certain elevation-the critical line for him. An elevation of 10,000 ft. or less may provoke it in some, others escape up to 14,000ft. , while a very few, possessed of unusual resisting power, can ascend to 19,000 ft. without much distress.

The acute form is characterized by a rapid pulse, nausea, vomiting, physical prostration, cyanosis, buzzing in the ears, dimmed sight, and fainting attacks. The symptoms of mountain sickness persist for one, two, or three days and then gradually disappear as the adaptive reactions to high altitude occur.

The essential cause of altitude sickness is lack of oxygen. The call for oxygen in the body comes from the active cells of the tissues. The place of oxidation is in the cells. Complete

deprivation of oxygen results in asphyxiation and death. The quantity of oxygen taken up by the cell depends on the needs of the cell, so long as the supply of oxygen is ample the cell takes what it needs and leaves the rest. Therefore, it is important that sufficient oxygen be available in the blood when the demand is made by the tissues. The rate of flow and the amount of oxygen passing from the blood to the tissues depends on the difference between the pressure of oxygen in the blood and in the tissue. The higher the oxygen pressure in the blood the greater will be the amount of oxygen passing from the blood of the capillaries into the tissues in a given unit of time. Oxygen diffuses from the place of higher pressure to the place of lower or no pressure. In the active tissues the oxygen tension is always low and it is usually supposed that there is then no oxygen pressure inside the cells. The dissociation of oxygen from the haemoglobin of the blood occurs with great rapidity, but it is greatest where the differences in pressure are the greatest. It follows, therefore, that the oxygen pressure in the blood must be sufficiently high to supply the needs of the cells in the brief interval of time that the blood is passing through the capillaries.

While all the tissues of the body are sensitive to oxygen want the nervous tissues are most sensitive. The adaptive responses to a lack of oxygen are undoubtedly initiated in the central nervous system.

The more definite changes in adaptation to altitude disclosed by experiment are: (1) An increase in the percentage and the total amount of haemoglobin in the blood and associated with this a redistribution of the red corpuscles whereby a reserve supply is

thrown into the general circulation; (2) a fall in the lung alveolar carbon dioxide pressure and a rise in the alveolar oxygen pressure, the result of increased ventilation of the lungs due to deeper breathing; (3) a rise in the arterial blood oxygen pressure which provides a partial pressure of oxygen in the blood much above the alveolar oxygen pressure; (4) an increase in the rate of blood flow. Each of these changes clearly assures a more adequate supply of oxygen for the tissues. The blood changes provide for more oxygen in a given unit volume of blood. The greater ventilation of the lungs permits a more thorough saturation of the haemoglobin with oxygen than would be possible if the oxygen pressure in the lungs decreased proportionately with the fall in barometric pressure. The rise in arterial blood oxygen pressure also means a greater saturation of the haemoglobin. The more rapid rate of blood flow raises to a limited extent the oxygen pressure in the blood passing through the tissues.

The percentage of haemoglobin at sea level varies between 94 and 106, average 100; at 6000 ft. average 110; at 14,000 ft. average 144.

The red corpuscles in the circulating blood vary at sea level between 4,500,000 and 5,500,000 per cubic millimeter; at 6000 ft. average 6,000,000; at 14,000 ft. average 7,100,000.

The oxygen content of arterial blood at sea level is 18 volumes percent; at 6000 ft. 20.8 percent; at 14,000 ft. 27.4 percent.

That the rate of blood flow is increased with altitude has been shown by Schneider and Sisco, who determined the rate of the blood flow through the hands. The flow through 100 cc. of hand

volume was shown to be from 30 to 70% greater on the summit of Pike's Peak than in Colorado Springs.

All adaptive changes occurring at high altitudes seem to be for the purpose of supplying more oxygen for the tissues. If, therefore, oxygen want is the cause of the increase observed in the flow of blood, it is to be expected that the inhalation of pure oxygen while at the high altitude may so benefit the body as to retard the heart and diminish the rate of the blood flow. Schneider and Sisco found that the breathing of an oxygen rich mixture while on Pike's Peak slowed the heart and decreased the rate of blood flow through the hands; from which we may conclude that lack of oxygen calls forth certain definite circulatory responses for the purpose of increasing the rate of blood flow, in order that the oxygen pressure may be sufficient to furnish the tissues with the oxygen they need as the blood passes through the capillaries.

It has been known since the researches of Haldane and his pupils, and more accurately since the studies made by Henderson, Haldane, Douglass and Schneider, that the volume of fresh air taken into the lungs per minute during rest is so regulated as to keep the partial pressure of carbon dioxide in the alveolar air practically constant for the individual. Therefore the carbon dioxide content of the alveolar air is taken as an index of lung ventilation. The breathing, however, is dependent on the integrity of a very small area, the respiratory center, of the brain. The reaction of this center is regarded as automatic, and any interference with its supply of properly aerated blood causes greatly increased activity and thereby increased breathing. Carbon dioxide in the blood is the stimulant which excites this

respiratory center and maintains its regular action. There is no doubt that slight changes in carbon dioxide in the blood affect the center, and a decrease in the amount of oxygen in the blood will also affect the respiratory center, It is generally held that the oxygen must be markedly lowered before the center begins to be stimulated by the decreasein oxygen.

In physiology it is found that the action of gases within the body is determined by the pressure and not by the percentage of gas. The percentage of alveolar carbon dioxide rises with the altitude, but as its partial pressure is determined by the barometric pressure we find that there is a fall in the alveolar carbon dioxide pressure as altitude increases. As the partial pressure of carbon dioxide in the alveolar air is about a third less on Pike's Peak than at sea level (about 27 mm. as compared with 40mm,) itiis evident that the alveolar ventilation for an equal production of carbon dioxide is about 30% greater on Pike's Peak.

To explain the fall in alveolar carbon dioxide pressure and the increased ventilation of the lungs at high altitudes it is necessary to consider the changes that occur in the blood. Want of carbon dioxide would, other things being equal, affect the affinity of the blood for oxygen. Decreased carbon dioxide alone in the blood would increase the affinity of the blood for oxygen. However, with the increase in altitude it is found that the affinity of the blood for oxygen remains approximately unaltered in spite of the lower carbon dioxide tension. This suggests that as one ascends the carbon dioxide in the blood is replaced by something else which produces an equal effect on the affinity of the haemoglobin for oxygen. A study of the dissociation curve of the blood made by Barcroft at various altitudes indicates that

there is an increase in the acid radicals, or a decrease in the bases of the blood. The higher the altitude reached the more marked is the acidosis, but at any given altitude the acidosis and the diminution of carbon dioxide so nearly balance each other that the reaction of the blood remains practically constant. Only a very careful study has been able to show that the increase of acidity is slightly in excess of the loss of carbon dioxide. This would lower the affinity of the blood for oxygen very slightly, but at the same time the change would be sufficient to give the increased stimulation to the respiratory center which would account for the increased ventilation of the lungs. What acid is responsible for the acidosis in the blood at high altitudes has not yet been acertained. It was once thought that lactic acid appeared in the blood with acclimatization to high altitude, but this is not maintained at present. It may be there is no increase of acid but a diminution in the amount of alkali present.

The passing of oxygen from the alveolar air into the blood of the lung capillaries may be wholly the result of diffusion, in which case it would pass from a place of high to one of low pressure. If oxygen passes from the alveoli only by diffusion the pressure of oxygen in the blood will always be less than, or at the best equal to, the alveolar oxygen tension. If the pressure of oxygen in the blood is under certain circumstances higher than that of the alveolar air there can be no doubt that forces other than diffusion must come into play. This would necessitate an active secretion by the epithelial cells of the lungs. Indirect evidence supports this theory of oxygen secretion. Haldane and his collaborators have found that at sea level muscular work may furnish a powerful stimulus to secretory absorption of oxygen by

the epithelial tissue of the lungs.

The acclimatization to oxygen want seen in mountaineers or persons living at high altitudes is evidently attributable to four factors: Increased breathing, increased percentage of haemoglobin, increased rate of blood flow, increased oxygen tension in the blood, as the result of increased activity of the lung epithelium. The longer the sojourn at a high altitude the more permanently fixed become the altitude adaptive changes. This fact has been proven by studies on the after effects of high altitudes in those who return to sea level. If the stay at the high altitude were of only a few days duration the blood returns almost immediately to its normal composition and the breathing likewise at once takes on the normal rate and depth. After five weeks on Pike's Peak the after effects were present for at least two weeks, and after a six months stay they persisted for ten weeks.

The study of the after effects indicates that the aviator remains at the high altitudes too short a period of time to secure permanent adaptive reactions which increase tolerance of high altitudes. The experience in aviation indicates that the changes in altitude during flying are made so rapidly that the compensating mechanisms for low oxygen are overworked to a greater or less degree, and as a consequence instead of securing acclimatization to low oxygen a weakening of the adjusting mechanism occurs which renders the flyer more liable to an attack of altitude sickness.

The ability to endure comfortably and well high altitudes is dependent upon the ease and quickness with which the adaptive responses in the breathing, the blood, and the circulation take

place. An explanation of the difference in reaction observed among the members of a group when at a high altitude is to be found in the degree of individual physical fitness. In persons damaged by disease, overwork, unhygienic living, or weakened by inactivity and by loss of sleep, the power of adjustment is as a rule below par.

In the field of aviation four problems demand solution:

1. The cause and nature of the failure , physiologic or psychologic, or both, on the part of the pilot which frequently precedes a fall.

2. The development of a method for determining the maximum altitude to which each individual pilot can ascend without danger of such failure.

3. The development of forms of physical training for increasing the resistance to the ill effects of altitude, and for maintaining the aviator in a state, not of acclimatization to high altitude like the mountaineer, but of the perfect physical condition of the athlete.

4. A better knowledge of the nature of air staleness- a condition closely similar to athletic overtraining.

It is with the first two of these problems that we are particularly concerned at present. For their study two forms of apparatus have been devised, a rebreathing machine and a low-pressure chamber. The rebreathing machine is an apparatus whereby the subject rebreathes a specified amount of air from a tank, thereby causing a gradual and progressive decrease of the oxygen. The carbon dioxide of the expired air is removed by sodium hydroxide and therefore is not a factor in the test. As the percentage of oxygen decreases the subject is physiologically ascending to higher altitudes. The volume of air rebreathing is

sufficient to require between 25 and 30 minutes to lower the amount of oxygen to 8% or 7%, which is equivalent to altitudes of 25,000 to 28,000 feet. The low pressure chamber may accommodate several persons at once, observers and subjects. The pressure is reduced by a motor driven vacuum pump and the observers are furnished with a supply of oxygen by individual tubes and mouthpieces connected to a main supply pipe passing through the wall of the chamber. Both tests are essentially low oxygen tests. The similarity and parallelism of the reactions in both tests upon the same individual are marked.

With regard to respiration it is the depth of breathing that ordinarily is increased by low oxygen. The majority of subjects show an increase in depth of from 20% to 128% when under from 8.5% to 6% of oxygen. The volume of each breath is found to range between 600cc. and 1250 cc. as compared with 360cc. to 640 cc. when breathing air of normal oxygen content. A good respiratory reaction is manifest in a slight increase in the depth of breathing, which begins at 16 or 15% of oxygen and continues progressively to increase slightly and gradually until from 12.5 to 9% of oxygen is reached. From there down to 8.5 and 6% of oxygen the volume of air breathed per minute increases much more rapidly due to greater depth and increased rate. The total increase per minute at the lower percentages of oxygen should be at least 5.5 liters.

Referring to the observations made on Pike's Peak, a study of the pulse rate during exposure to low oxygen should give a definite indication of the sensitiveness of the organism to low oxygen. This has been found to be true provided care is taken to have the subject calm and quiet at the beginning of the

experiment. Throughout the test the candidate's pulse is counted for a period of 30 seconds each minute, the systolic and diastolic blood pressures are determined every minute. Three types of circulatory reaction to oxygen want have been observed: The first, or best, in which the pulse accelerates moderately as the oxygen decreases, the systolic pressure is unchanged or shows a rise of not more than 20 or 30 mm. of mercury, and the diastolic pressure remains unchanged or rises slightly. The second, in which the pulse rate accelerates moderately and the systolic pressure rises as the diastolic pressure gradually falls. The third, in which after a period of fair, good, or excessive rsponse in the rate of the heart beat, the diastolic pressure suddenly falls, and soon thereafter the systolic pressure, and the pulse rate slows. This is called the fainting type. Those in the first class may tolerate as low an oxygen as 6% (equivalent to an altitude of 29,000 ft.), may lose consciousness without fainting and recover quickly when restored to air, while the pulse rate and blood pressure are soon back to normal. The fainting type rarely can endure so low an oxygen and if allowed to go on faint completely, revives slowly, and requires an hour or two to regain normal pulse rate and blood pressure.

Observations show that during short exposures to high altitudes such as the aviator experiences the compensatory reactions of the body to a decreased oxygen are made almost entirely by the circulation and by the respiration. A few men may, after an hour or more, secure some benefit from a slowly developing concentration of the haemoglobin of the blood.

It is to be assumed, of course, that no organism will fail to make some effort to adjust itself to altered conditions.

Occasionally individuals are found whose reactions are almost nil. Such men show no demonstrable rise in pulse rate, no change in blood pressures or in respiration. From this it can be predicted that the psychological tests will show early deterioration. In addition to those who are constitutionally inferior similar lack of reaction will be shown by many men, especially those toward middle age, who have led a sedentary life, are overweight and flabby. It is not to be expected that either of these types will commonly be found among a class of men so carefully selected as aviators, but lesser degrees of inability to compensate are not uncommonly found.

Those men who are the best type for aviation compensate fully to great altitudes, retain their efficiency, and yet do this in so accurate and economical a manner from the point of view of the circulation that there is little or no evidence of strain. When the break comes (usually above 25,000 ft. or from 5.5 to 7% oxygen) it comes with great suddenness; from almost full efficiency there is a lapse into unconsciousness, but without circulatory collapse. There is no loss of general muscular tone, recovery is almost instantaneous on return to normal oxygen pressure and is complete. The subject usually refuses to believe that he has not been conscious and efficient throughout. This unconsciousness is to be attributed to direct action of low oxygen on the cortical centers.

Quite different is the picture when circulatory failure has occurred; cardiac dilatation, sudden collapse of vascular tone, ashy color, cold sweat, loss of muscular tone, so that the subject falls from his seat. Recovery is slow and unsatisfactory.

The syndrome of heart strain, followed by dilatation and fainting, is of very great importance in aviation. We know that fainting in the air is common and that such an occurrence is practically always fatal. We know also that aviators almost invariably develop in time a staleness, which is strongly suspected to be the result of this recurring heart strain, and that fliers who have gone stale are particularly sensitive to low oxygen and particularly liable to dilatation and fainting.

The essential difference between the best type and the next to best type is partly strength and quality of the heart muscle, it is partly a smooth working of the nervous regulation of heart and blood vessels, including freedom from high nervous tension, it is partly the ability to furnish an abundant circulation through the coronary vessels when the need arises. It can be expressed in the word "condition". The necessity is emphasized for keeping aviators as nearly as possible in perfect physical condition and preventing them from flying when they are not so.

The test for the classification of aviators is an outgrowth of the research work on the physiological effects of low atmospheric pressure. With the finding of such wide variations in the resistance to this condition the task was undertaken of determining which individuals were most suitable for the branches of work which involve flying to the higher altitudes. In the first place are the fighters who commonly fly between 15,000 and 20,000 feet; in the second the bombers, who fly comparatively high but rarely above 15,000 feet; and third, the observation planes that rarely go above 10,000 feet. The results of the test are expressed in the ratings A, B, and C, corresponding to the above

requirements. Class D includes men who ought not to fly at all.

The routine test is carried out as follows: A careful history is recorded and a general physical examination made with particular attention to pulse and blood pressure before and after moderate exercise. The rebreathing machine is adjusted so that the run will be between 25 and 30 minutes. During the run the subject does prescribed psychological work and is carefully observed by the psychologist to determine the earliest effects on attention and motor co-ordination, as well as the time of appearance of more marked effects and total breakdown. Every three minutes the capacity of the external and internal ocular muscles is tested (near point of convergence and near point of accommodation). Pulse and blood pressure are measured every one or two minutes. The heart is frequently examined by the clinician and the respiration is recorded on a kymograph. The test ends when the psychologist determines that the subject has reached the point of complete inefficiency or the clinician finds that the condition of the circulation makes prolongation of the test undesirable. At the close the air remaining in the apparatus is analyzed to determine the oxygen percentage reached. The results of the test are summarized in a plot of which the abscissa line represents minutes of time and the ordinates are percent of oxygen, pulse, blood pressure, volume of respiration, etc. The decision of the rating of the subject is made by consensus of opinion and is ordinarily the lowest rating assigned by any department.

Aside from ocular deficiencies or general physical conditions of a distinctly abnormal nature, the rating of a subject depends on the answer to two questions: How well does he adapt himself

to the unusual environment, i. e., how well does he preserve his efficiency at altitudes as expressed by the psychological tests; and second, at the expense of how much strain on his circulatory system does he do it? The ratings of several hundred men examined (374) show the percentage in each class to be as follows: A- 40.5%, B- 34.6%, C- 20.3%, D- 4.8%.

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THE INFLUENCE OF INTERNAL SECRETIONS ON THE FORMATION OF BILE

BY

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The experiments that form the basis of the present report were undertaken in an effort to determine the effect of certain of the glands of internal secretion upon the output of bile by the hepatic cells. For our study we selected the following gland substances: mammary, orchic, ovarian, pancreatic, splenic, thymic and thyroid. These were all obtained from Armour & Company. To the foregoing list we added solution of adrenalin chloride, prepared by Parke, Davis & Company, and secretin, prepared by the method we have described in connection with other experiments (1).

The procedure was the same in all of the experiments: The animal to be operated upon, usually a dog but in a few cases a cat, was anesthetized by morphine and ether, if a dog, or by ether alone, if a cat; a cannula was inserted in the left carotid artery and connection made with a mercury manometer in order to record blood pressure; another cannula was inserted in the right external jugular vein for the injection of a solution of the gland substance being studied. The abdomen was opened in the linea alba and a third cannula, specially constructed, was tied in the common bile duct; the cystic duct was now clamped or ligated, the edges of the abdominal incision brought together, and a towel wrung out in physiological saline solution at a temperature of 40°C. placed upon the abdomen so as to cover the wound completely. This towel was kept moist. Rectal temperature was taken from the time the anesthetic was started until the end of the experiment. An electrically heated operating table was used.

When all was in readiness an observer, who had no other duty, began to count the drops of bile as they fell from the end of the cannula tied in the common duct. All counts were made for an arbitrary period of twenty minutes. The first count was made before any agent was injected. When this initial count was finished the gland substance to be

studied was injected per jugular. In every case, except the experiments with adrenalin, a dose of 10 mgm. of the gland substance per kilogram of body weight of the animal was dissolved in 100 cc. of physiological saline solution, warmed to 37°C. on a water bath, and injected by means of a burette. The counting of the drops of bile was continued for a second twenty-minute period beginning at the moment the injection of the gland substance started. In most instances another twenty-minute count was made, giving an initial count with which comparison could be made and one or two counts after the gland substance had been administered.

No attempt was made to analyze the bile at any time during the course of any experiment so that we are unable to speak with regard to qualitative changes that may have resulted. The number of drops of bile secreted in each period may be regarded as indicative of the activity of the liver cells so far as bile production is concerned during that particular time and it was to this that our inquiry was directed.

The results of all the experiments have been arranged in groups, each group comprising the determinations made with one gland substance, and these are presented in the accompanying tables.

Adrenalin (table 1) produced a decrease during the first twenty minutes in every case. There were three occasions on which it was possible to make a second count after the injection and in two of these the number of drops of bile secreted was still less than during the period of the initial count.

Eight determinations were made with mammary gland substance (table 2); five showed a decrease from the initial count during the first twenty-minute period, two an increase and one no change. Where a second count was made after the injection, which was done in seven of the experiments, no definite trend was observable. It would seem that the effect of mammary gland substance on the secretion of bile is a temporary decrease.

Orchic substance (table 3) caused a lessened secretion of bile during the first twenty minutes after the injection in five out of seven experiments; in four of the five the effect was progressive, a further decrease occurring in the second twenty minutes.

In the five tests made with ovarian substance (table 4) there was a decrease in every instance, averaging 44.59 per cent in the first twenty minutes, and 59.36 per cent in the second twenty minutes.

Pancreas (table 5) was injected into nine dogs and the count of the drops of bile during the succeeding twenty minutes revealed a decrease

TABLE 1

Adrenalin. Dose: 0.1 cc. of a 1: 1,000 solution adrenalin chloride per kilogram of body weight

EXPERIMENT NUMBER	INITIAL COUNT	1ST COUNT AFTER INJECTION	PERCENTAGE EFFECT	2ND COUNT AFTER INJECTION	PERCENTAGE EFFECT
	drops	*drops*		*drops*	
7 (cat)	10	4	−60.00	5	−50.00
13	140	49	−65.00	No count	
27	9	8	−11.11	13	+44.44
47	16	12	−25.00	9	−43.75
60	13	10	−23.07	No count	

TABLE 2

Mammary substance. Dose: 10 mgm. per kilogram of body weight

EXPERIMENT NUMBER	INITIAL COUNT	1ST COUNT AFTER INJECTION	PERCENTAGE EFFECT	2ND COUNT AFTER INJECTION	PERCENTAGE EFFECT
	drops	*drops*		*drops*	
8	3	2	−33.33	2	− 33.33
11	46	23	−50.00	No count	
16	18	5	−72.22	2	− 88.88
25	5	5	00.00	15	+200.00
34 (cat)	6	7	+16.66	10	+ 66.66
46	15	12	−20.00	22	+ 46.66
49 (cat)	10	15	+50.00	14	+ 40.00
57	22	13	−40.90	5	− 77.27

TABLE 3

Orchic substance. Dose: 10 mgm. per kilogram of body weight

EXPERIMENT NUMBER	INITIAL COUNT	1ST COUNT AFTER INJECTION	PERCENTAGE EFFECT	2ND COUNT AFTER INJECTION	PERCENTAGE EFFECT
	drops	*drops*		*drops*	
4	84	45	−46.42	23	−72.61
18	31	3	−90.32	35	+12.90
19	134	15	−88.80	9	−93.20
41	35	12	−65.71	4	−88.57
42	9	8	−11.11	4	−55.55
55	12	25	+108.33	No count	
62	25	35	+40.00	No count	

TABLE 4

Ovarian substance. Dose: 10 mgm. per kilogram of body weight

EXPERIMENT NUMBER	INITIAL COUNT	1ST COUNT AFTER INJECTION	PERCENTAGE EFFECT	2ND COUNT AFTER INJECTION	PERCENTAGE EFFECT
	drops	*drops*		*drops*	
5	19	18	−5.26	10	−47.36
20	35	8	−77.14	4	−88.57
43	4	1	−75.00	3	−25.00
56	30	27	−10.00	15	−50.00
59	9	4	−55.55	1	−88.88

TABLE 5

Pancreatic substance. Dose: 10 mgm. per kilogram of body weight

EXPERIMENT NUMBER	INITIAL COUNT	1ST COUNT AFTER INJECTION	PERCENTAGE EFFECT	2ND COUNT AFTER INJECTION	PERCENTAGE EFFECT
	drops	*drops*		*drops*	
1	16	3	−81.25	3	−81.25
14	89	60	−32.58	42	−52.80
22	35	15	−57.11	No count	
23	121	108	−10.74	73	−39.66
30	3	2	−33.33	2	−33.33
38	42	22	−47.61	25	−40.47
48	8	3	−62.50	3	−62.50
50	25	17	−32.00	25	00.00
52	25	12	−52.00	No count	

TABLE 6

Secretin. Dose: 10 mgm. of a dried acid extract per kilogram of body weight

EXPERIMENT NUMBER	INITIAL COUNT	1ST COUNT AFTER INJECTION	PERCENTAGE EFFECT	2ND COUNT AFTER INJECTION	PERCENTAGE EFFECT
	drops	*drops*		*drops*	
9	31	35	+12.90	36	+16.12
10	1	6	+500.00	4	+300.00
15	2	6	+200.00	36	+1700.00
26	1	6	+500.00	1	00.00
35	36	64	+77.77	55	+52.77
36	4	18	+350.00	No count	
54	2	3	+50.00	No count	

TABLE 7

Splenic substance. Dose: 10 mgm. per kilogram of body weight

EXPERIMENT NUMBER	INITIAL COUNT	1ST COUNT AFTER INJECTION	PERCENTAGE EFFECT	2ND COUNT AFTER INJECTION	PERCENTAGE EFFECT
	drops	*drops*		*drops*	
2	198	198	00.00	207	+4.54
21	89	45	−49.43	30	−66.29
24	4	8	+100.00	6	+50.00
31	207	205	−0.96	No count	
44	36	19	−47.22	20	−44.44
45	6	7	+16.66	6	00.00
61	37	18	−51.35	7	−81.08

TABLE 8

Thymic substance. Dose: 10 mgm. per kilogram of body weight

EXPERIMENT NUMBER	INITIAL COUNT	1ST COUNT AFTER INJECTION	PERCENTAGE EFFECT	2ND COUNT AFTER INJECTION	PERCENTAGE EFFECT
	drops	*drops*		*drops*	
3	55	18	−67.27	61	+10.90
29 (cat)	42	38	−9.52	No count	
32	37	17	−54.05	13	−64.86
39	45	17	−62.22	31	−31.11
53	31	7	−77.41	2	−93.54

TABLE 9

Thyroid substance. Dose: 10 mgm. per kilogram of body weight

EXPERIMENT NUMBER	INITIAL COUNT	1ST COUNT AFTER INJECTION	PERCENTAGE EFFECT	2ND COUNT AFTER INJECTION	PERCENTAGE EFFECT
	drops	*drops*		*drops*	
6	8	10	+25.00	6	−25.00
12	24	13	−45.83	17	−29.16
17	20	11	−45.00	9	−55.00
28	3	10	+233.33	6	+100.00
33	6	5	−16.66	3	−50.00
37	17	15	−11.76	16	− 5.88
40	9	12	+33.33	8	−11.11
51	16	22	+37.50	No count	
58	8	4	−50.00	No count	

in all. The average decrease was 45.45 per cent. A further count was made in seven of these experiments and showed the effect to be maintained in all but one. The average decrease for this period below the initial count was 44.28 per cent.

In the seven cases in which secretin (table 6) was administered intravenously there was a marked augmentation in the amount of bile secreted. This increase averaged 241.52 per cent. A subsequent count was made on five occasions and in four of these the output of bile was still above the original level. Experiment 15 of this group is particularly striking; during the second period after the injection the amount of bile formed was six times as great as that during the first period and eighteen times that produced in the twenty minutes immediately preceding the giving of the secretin. The effect of secretin on this group of dogs is further confirmation of the results reported by Bayliss and Starling (2).

Splenic substance (table 7) was administered to seven animals and failed to exhibit any constant effect.

Thymus gland substance (table 8) uniformly brought about a decrease in the quantity of the biliary secretion during the first period after it was injected. This effect was still evident in three out of four experiments in which a second count after injection was made.

Intravenous injection of the substance of the thyroid gland (table 9), like splenic substance, was without constant effect.

A review of the literature has failed to reveal the report of any definite experiments with regard to the influence of the internal secretions on the amount of bile secreted. In a study of bile pigment metabolism Hooper and Whipple (3) state that in two groups of dogs, the members of one group having undergone splenectomy and those of the other group serving as controls, the quantity of bile pigment and of bile produced was identical. This result is in accord with our finding that splenic substance intravenously did not alter definitely the output of bile.

CONCLUSIONS

1. The amount of bile secreted is increased by secretin.
2. The amount of bile secreted is decreased by adrenalin and by mammary, orchic, ovarian, pancreatic and thymic gland substances.
3. The amount of bile secreted is not affected in a constant or definite manner by the substance of the spleen and thyroid gland.

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THE INFLUENCE OF SECRETIN ON THE NUMBER OF ERYTHROCYTES IN THE CIRCULATING BLOOD

BY

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In 1895 Dolinski (1) showed that acids brought into contact with the mucous membrane of the duodenum set up a secretion of pancreatic juice. Pawlow and his co-workers (2) further decided that the acid acts reflexly through a nerve center. Later Popielski (3), working under the direction of Pawlow, showed that if acids are introduced into the duodenum the pancreatic secretion appears after resection of both vagus and splanchnic nerves, after extirpation of the solar plexus and even after destruction of the spinal cord. He concluded that the secretion arose from a peripheral reflex through scattered ganglia of the pancreas, situated mostly near the duodenum. The same results and conclusions were reached by Wertheimer and Lepage (4). At this point Bayliss and Starling (5) demonstrated the true explanation of the phenomenon. They showed that the acid acts on a substance in the duodenal mucous membrane, prosecretin, and changes it into another substance, secretin. This is carried by the blood and activates the pancreatic cells.

Bayliss and Starling (5) also showed that secretin increases the secretion of bile. We have confirmed this by noting the rate of flow of bile incidentally in the course of other experiments. Sir Edward A. Schäfer (6) states that secretin increases the flow of bile and of succus entericus but to a less extent than it affects the flow of pancreatic juice. He also states that intravenous injection of duodenal extract (evidently secretin from the context) has been shown by Cow (7) to cause the appearance of the pituitary autacoids in the cerebro-spinal fluid.

Beveridge and Williams (8) in their very ingenious exposition of what they call the proteomorphic theory of immunity claim to have the records of over two hundred cases of diabetes and exophthalmic goiter in which the number of red corpuscles per cubic millimeter of

blood was increased by the administration of secretin. Their theory of the production of immunity depends greatly on the power to hydrolyze proteins which they attribute to the red blood corpuscles. If we grant that these premises are correct, then any agent capable of bringing about a sufficient increase in the number of the red corpuscles becomes of therapeutic value. We have been unable to obtain details of the records to which reference has been made. If secretin is to exert any influence as an immunizing agent by increasing the number of red corpuscles in the circulating blood, it is obvious that a single dose must be capable of causing a great and fairly prolonged rise in the red corpuscle count. As a means of ordinary treatment, hypodermic medication is preferable to intravenous, and if it can be shown that secretin administered hypodermically is able to increase the number of red corpuscles, then again, in order to be of service, a single dose, or at most three or four successive doses, should produce and maintain a largely increased erythrocyte count.

Acting in accordance with the ideas thus suggested we determined to try first, the effect of a certain arbitrarily fixed dose of secretin given intravenously and second, the effect of the same dose when introduced hypodermatically.

In our selection of the animal to be used we were guided by the recent work of Lamson (9) on acute polycythemia in which he has shown that adrenalin, fright, pain, etc., cause sudden and very marked elevation of the red corpuscle count in the dog and cat but that these agents are without effect on the erythrocyte count of the rabbit. Therefore, that we might avoid the use of an anaesthetic, especially in those experiments which were to be continued over several days, in order that the attending conditions might be as uniform as possible, rabbits were employed in all of the experiments recorded in this paper.

The secretin was in all cases prepared from the intestine of the dog. The animal was anaesthetized by ether alone and the upper half of the small intestine removed. This intestine was carefully washed in running water and the mucous membrane scraped off with a dull knife. The scrapings were rubbed up in a mortar with sand, covered with 50 cc. of 0.4 per cent hydrochloric acid and allowed to stand for an hour or more. The mixture was then boiled actively for several minutes, neutralized with strong potassium hydroxide while boiling and again rendered faintly acid with glacial acetic acid. Finally the preparation was strained through muslin and filtered.

We found that this preparation when kept in the dark retained its

potency for about five days; but if glacial acetic acid were added to the filtrate in sufficient quantity to make this 2 per cent acid by volume and the solution evaporated to dryness, the residue was found to retain its potency for months at least. When required, a weighed quantity could be dissolved in distilled water and neutralized, thus giving a preparation of the same effectiveness as the original solution.

Over two hundred determinations of the red corpuscles per cubic millimeter of blood were made in the course of these experiments, the blood being obtained from the ear of the rabbit and the count made in the usual manner with the Thoma-Zeiss apparatus.

The dose of secretin solution selected for the first experiments was 1 cc. per kilogram of body weight. Five rabbits were taken, the erythrocytes per cubic millimeter of blood counted, and the proper dose of secretin injected into the femoral vein. The results of these experiments are recorded in table 1.

TABLE 1

Dose: 1 cc. secretin solution per kilogram of body weight

EXPERIMENT NUMBER	INITIAL COUNT	MAXIMUM COUNT	AMOUNT OF INCREASE	PERCENTAGE INCREASE	MAXIMUM IN	DURATION OF EFFECT
					minutes	*minutes*
1	5,320,000	7,510,000	2,190,000	41.16	30	60
2	4,560,000	6,990,000	2,430,000	53.29	15	70
3	4,450,000	6,350,000	1,900,000	42.69	40	65
4	5,610,000	8,210,000	2,600,000	46.35	45	90
5	4,830,000	5,630,000	800,000	16.56	25	45
Averages....	4,954,000	6,938,000	1,984,000	40.04	31	66

As a type of this series of experiments the first one is given in detail:

Experiment 1, November 6, 1916

10.05 a.m. Red blood corpuscles, 5,320,000 per cubic millimeter
10.10 a.m. 1 cc. secretin per kilogram of body weight given intravenously
10.25 a.m. Red blood corpuscles, 6,940,000 per cubic millimeter
10.40 a.m. Red blood corpuscles, 7,510,000 per cubic millimeter
10.55 a.m. Red blood corpuscles, 7,120,000 per cubic millimeter
11.10 a.m. Red blood corpuscles, 5,350,000 per cubic millimeter
11.30 a.m. Red blood corpuscles, 5,290,000 per cubic millimeter

The next thing to be determined was the effect of the same dose upon the number of red corpuscles when it was introduced beneath

the skin. A tabulated report of the results obtained in this way will be found in table 2.

TABLE 2

Dose: 1 cc. secretin solution per kilogram of body weight

EXPERIMENT NUMBER	INITIAL COUNT	MAXIMUM COUNT	AMOUNT OF INCREASE	PERCENTAGE INCREASE	MAXIMUM IN	DURATION OF EFFECT
					minutes	*minutes*
6	5,120,000	6,305,000	1,185,000	23.1	60	90
7	4,548,000	5,844,000	1,296,000	28.4	30	30
8	4,536,000	5,545,000	1,009,000	22.2	30	90
9	4,906,000	5,619,000	713,000	14.5	55	95
10	5,840,000	7,197,000	1,357,000	23.2	60	90
Averages....	4,990,000	6,102,000	1,112,000	22.2	47	79

As typical of this series of experiments the first one is here presented in detail:

Experiment 6, November 20, 1916

1.30 p.m. Red blood corpuscles, 5,120,000 per cubic millimeter
1.35 p.m. 1 cc. secretin per kilogram of body weight given hypodermatically
2.05 p.m. Red blood corpuscles, 5,336,000 per cubic millimeter
2.35 p.m. Red blood corpuscles, 6,305,000 per cubic millimeter
3.35 p.m. Red blood corpuscles, 5,601,000 per cubic millimeter
4.35 p.m. Red blood corpuscles, 5,006,000 per cubic millimeter

A comparison of the results obtained in these two groups of experiments shows certain features in favor of the intravenous method of administration. The most striking difference is in the percentage increase—an average of 40 per cent when the secretin is given intravenously and 22.2 per cent when given hypodermatically. However, if we note the average actual increase in number of red corpuscles the difference is only slightly over one-half million in favor of the intravenous method—1,984,000 in the former case and 1,112,000 in the latter. As might be expected the intravenous method gives the effect in a shorter time than the subcutaneous,—the maximum effect obtained in thirty-one minutes in one instance and in forty-seven minutes in the other; but when we compare the duration of the effect we find it almost identical in the average of the two groups—sixty-six minutes was the average time that the increase lasted when the secretin was given intravenously and seventy-nine minutes when it was given hypodermatically.

The second group of experiments had convinced us that secretin injected subcutaneously was capable of exerting an influence, at least so far as affecting the number of red corpuscles in circulation was concerned. Moreover, the greater effect obtained by giving the secretin intravenously was not sufficiently pronounced to make it the method of choice so far as any therapeutic application was concerned. Therefore, we decided to adhere to the method of hypodermic administration in the remainder of our experiments, particularly as these two series of observations appeared to furnish sufficient data from which to deduce the probable action of any particular dose of secretin when given intravenously if we had determined its effect when given hypodermatically.

To determine the most effective dose we made several series of experiments using the following doses per kilogram of body weight: 0.75 cc., 0.5 cc., 0.25 cc., 1.5 cc., 2 cc. In this way we tested the effect of amounts of secretin less than and greater than the original and arbitrary dose of 1 cc. per kilogram of body weight. Each group table gives the summarized results of each experiment in the group and the averages for that particular series. Following each group summary is a report giving the details of one experiment in the group, serving as an example of all.

TABLE 3

Dose: 0.75 cc. secretin solution per kilogram of body weight

EXPERIMENT NUMBER	INITIAL COUNT	MAXIMUM COUNT	AMOUNT OF INCREASE	PERCENTAGE INCREASE	MAXIMUM IN	DURATION OF EFFECT
					minutes	*minutes*
13	5,327,000	6,224,000	897,000	16.8	60	90
14	6,334,000	7,168,000	834,000	13.1	30	30
20	6,384,000	7,098,000	714,000	11.0	60	60
21	5,324,000	6,961,000	1,637,000	30.7	90	90
Averages....	5,842,250	6,862,750	1,020,500	17.9	60	67.5

Experiment 13, January 12, 1917

9.30 a.m. Red blood corpuscles, 5,327,000 per cubic millimeter
10.20 a.m. 0.75 cc. secretin per kilogram of body weight given hypodermatically
10.50 a.m. Red blood corpuscles, 5,206,000 per cubic millimeter
11.20 a.m. Red blood corpuscles, 6,224,000 per cubic millimeter
12.20 p.m. Red blood corpuscles, 6,042,000 per cubic millimeter
1.20 p.m. Red blood corpuscles, 5,100,000 per cubic millimeter

TABLE 4

Dose: 0.5 cc. secretin solution per kilogram of body weight

EXPERIMENT NUMBER	INITIAL COUNT	MAXIMUM COUNT	AMOUNT OF INCREASE	PERCENTAGE INCREASE	MAXIMUM IN	DURATION OF EFFECT
					minutes	*minutes*
16	6,251,000	6,837,000	586,000	9.3	30	30
19	5,741,000	7,875,000	2,134,000	37.1	90	90
24	6,048,000	No effect				
30	5,804,000	No effect				
31	6,760,000	7,046,000	286,000	4.2	60	60
Averages....	6,120,800	6,722,000	601,200	10.1	36	36

Experiment 16, January 22, 1917

12.55 p.m. Red blood corpuscles, 6,251,000 per cubic millimeter
1.00 p.m. 0.5 cc. secretin per kilogram of body weight given hypodermatically
1.30 p.m. Red blood corpuscles, 6,837,000 per cubic millimeter
2.00 p.m. Red blood corpuscles, 6,079,000 per cubic millimeter
3.00 p.m. Red blood corpuscles, 6,426,000 per cubic millimeter

TABLE 5

Dose: 0.25 cc. secretin solution per kilogram of body weight

EXPERIMENT NUMBER	INITIAL COUNT	MAXIMUM COUNT	AMOUNT OF INCREASE	PERCENTAGE INCREASE	MAXIMUM IN	DURATION OF EFFECT
					minutes	*minutes*
11	5,888,000	6,810,000	922,000	15.6	30	30
17	5,754,000	No effect				
18	5,280,000	6,144,000	864,000	16.3	30	30
25	4,075,000	5,015,000	940,000	23.1	30	30
27	5,970,000	No effect				
Averages....	5,395,000	5,940,200	545,200	11.0	18	18

Experiment 11, November 28, 1916

1.10 p.m. Red blood corpuscles, 5,888,000 per cubic millimeter
1.15 p.m. 0.25 cc. secretin per kilogram of body weight given hypodermatically
1.45 p.m. Red blood corpuscles, 6,810,000 per cubic millimeter
2.15 p.m. Red blood corpuscles, 5,988,000 per cubic millimeter

TABLE 6

Dose: 1.5 cc. secretin solution per kilogram of body weight

EXPERIMENT NUMBER	INITIAL COUNT	MAXIMUM COUNT	AMOUNT OF INCREASE	PERCENTAGE INCREASE	MAXIMUM IN	DURATION OF EFFECT
					minutes	*minutes*
12	6,376,000	7,440,000	1,064,000	15.1	60	90
22	7,188,000	No effect				
28	4,959,000	7,162,000	2,203,000	44.8	120	120
32	5,936,000	7,416,000	1,480,000	24.9	60	90
Averages....	6,114,750	7,301,500	1,186,750	21.2	58	60

Experiment 12, December 20, 1916

10.00 a.m. Red blood corpuscles, 6,376,000 per cubic millimeter
10.30 a.m. 1.5 cc. secretin per kilogram of body weight given hypodermatically
11.00 a.m. Red blood corpuscles, 6,937,000 per cubic millimeter
11.30 a.m. Red blood corpuscles, 7,440,000 per cubic millimeter
12.30 p.m. Red blood corpuscles, 6,014,000 per cubic millimeter

TABLE 7

Dose: 2 cc. secretin solution per kilogram of body weight

EXPERIMENT NUMBER	INITIAL COUNT	MAXIMUM COUNT	AMOUNT OF INCREASE	PERCENTAGE INCREASE	MAXIMUM IN	DURATION OF EFFECT
					minutes	*minutes*
15	4,112,000	5,188,000	1,076,000	26.1	30	60
23	5,928,000	6,935,000	1,007,000	16.9	30	90
26	5,858,000	6,471,000	613,000	10.4	30	90
29	5,400,000	7,502,000	2,102,000	38.9	60	120
Averages....	5,324,500	6,524,000	1,199,500	22.4	37.5	90

Experiment 15, January 12, 1917

9.20 a.m. Red blood corpuscles, 4,112,000 per cubic millimeter
9.30 a.m. 2 cc. secretin per kilogram of body weight given hypodermatically
10.00 a.m. Red blood corpuscles, 5,188,000 per cubic millimeter
10.30 a.m. Red blood corpuscles, 4,507,000 per cubic millimeter
11.30 a.m. Red blood corpuscles, 4,207,000 per cubic millimeter

As we proceeded with our observations the results pointed to a dose of 1 cc. per kilogram of body weight as being the most efficient. In order to assure ourselves on this point we made seven more experiments in which the dose was 1 cc. per kilogram of body weight. Taken to-

gether with the five original experiments recorded in table 2 we have a total of twelve such determinations. For the purpose of computing an average with as large a number of experiments as possible these have been brought together in table 8.

TABLE 8

Dose: 1 cc. secretin solution per kilogram of body weight

EXPERIMENT NUMBER	INITIAL COUNT	MAXIMUM COUNT	AMOUNT OF INCREASE	PERCENTAGE INCREASE	MAXIMUM IN	DURATION OF EFFECT
					minutes	*minutes*
6	5,120,000	6,305,000	1,185,000	23.1	60	90
7	4,548,000	5,844,000	1,296,000	28.4	30	30
8	4,536,000	5,545,000	1,009,000	22.2	30	90
9	4,906,000	5,619,000	713,000	14.5	55	95
10	5,840,000	7,197,000	1,357,000	23.2	60	90
33	5,778,000	6,894,000	1,116,000	19.3	30	90
34	5,872,000	6,579,000	707,000	12.0	50	70
35	6,200,000	6,850,000	650,000	10.4	50	90
36	5,456,000	5,955,000	499,000	9.1	70	80
37	5,200,000	7,240,000	2,040,000	39.2	25	105
38	4,720,000	7,264,000	2,544,000	53.8	75	30
39	5,684,000	6,752,000	1,068,000	18.7	35	30
Averages....	5,321,666	6,503,666	1,182,000	22.2	47.5	73.3

Reviewing the average percentage increase with each dose we find the results to have been as follows: 0.25 cc. secretin per kilogram of body weight, 11.0 per cent; 0.5 cc. secretin per kilogram of body weight, 10.1 per cent; 0.75 cc. secretin per kilogram of body weight, 17.9 per cent; 1 cc. secretin per kilogram of body weight, 22.2 per cent; 1.5 cc. secretin per kilogram of body weight, 21.2 per cent; 2 cc. secretin per kilogram of body weight, 22.4 per cent. These records indicate a dose of 1 cc. per kilogram of body weight as the most efficient dose of secretin. We also find that the longest average time the effect lasted was ninety minutes—where the dose was 2 cc. secretin per kilogram of body weight. With a dose of 1 cc. per kilogram of body weight the average duration was 73.3 minutes. It seemed worth while to test the effect of repeated doses of secretin on the increase in the number of erythrocytes per cubic millimeter of blood, both as to the amount of increase and the duration of the increase. Is it possible to produce a summation effect? To answer this question the following experiments were performed: One in which a dose of 1 cc. secretin per kilogram of

body weight was followed in two hours by a second dose of 1 cc. per kilogram of body weight; two experiments in each of which four successive doses of 1 cc. secretin per kilogram of body weight were administered at intervals of one hour; one experiment in which five successive doses of 1 cc. secretin per kilogram of body weight were given at intervals of one hour; one experiment in which five successive doses of 1 cc. secretin per kilogram of body weight were given at intervals of twenty-four hours. The results of these observations are appended.

Experiment 40, February 14, 1917

9.45 a.m. Red blood corpuscles, 4,548,000 per cubic millimeter
10.00 a.m. 1 cc. secretin per kilogram of body weight given hypodermatically
10.30 a.m. Red blood corpuscles, 5,844,000 per cubic millimeter
11.00 a.m. Red blood corpuscles, 5,338,000 per cubic millimeter
12.00 noon Red blood corpuscles, 5,025,000 per cubic millimeter
12.30 p.m. 1 cc. secretin per kilogram of body weight given hypodermatically
1.00 p.m. Red blood corpuscles, 5,042,000 per cubic millimeter
2.00 p.m. Red blood corpuscles, 5,600,000 per cubic millimeter
3.00 p.m. Red blood corpuscles, 5,787,000 per cubic millimeter

February 15, 1917

10.00 a.m. Red blood corpuscles, 4,286,000 per cubic millimeter

February 16, 1917

10.00 a.m. Red blood corpuscles, 4,457,000 per cubic millimeter

Experiment 41, February 19, 1917

9.55 a.m. Red blood corpuscles, 5,765,000 per cubic millimeter
10.00 a.m. 1 cc. secretin per kilogram of body weight given hypodermatically
10.55 a.m. Red blood corpuscles, 7,094,000 per cubic millimeter
11.00 a.m. 1 cc. secretin per kilogram of body weight given hypodermatically
11.55 a.m. Red blood corpuscles, 6,756,000 per cubic millimeter
12.00 noon 1 cc. secretin per kilogram of body weight given hypodermatically
12.55 p.m. Red blood corpuscles, 7,459,000 per cubic millimeter
1.00 p.m. 1 cc. secretin per kilogram of body weight given hypodermatically
2.00 p.m. Red blood corpuscles, 8,327,000 per cubic millimeter
3.00 p.m. Red blood corpuscles, 6,749,000 per cubic millimeter
4.00 p.m. Red blood corpuscles, 6,195,000 per cubic millimeter

February 20, 1917

9.00 a.m. Red blood corpuscles, 6,156,000 per cubic millimeter

February 21, 1917

9.00 a.m. Red blood corpuscles, 5,832,000 per cubic millimeter

Experiment 42, February 20, 1917

8.55 a.m. Red blood corpuscles, 5,245,000 per cubic millimeter
9.00 a.m. 1 cc. secretin per kilogram of body weight given hypodermatically
9.55 a.m. Red blood corpuscles, 5,645,000 per cubic millimeter
10.00 a.m. 1 cc. secretin per kilogram of body weight given hypodermatically
10.55 a.m. Red blood corpuscles, 6,723,000 per cubic millimeter
11.00 a.m. 1 cc. secretin per kilogram of body weight given hypodermatically
11.55 a.m. Red blood corpuscles, 6,659,000 per cubic millimeter
12.00 noon 1 cc. secretin per kilogram of body weight given hypodermatically
1.00 p.m. Red blood corpuscles, 6,384,000 per cubic millimeter
2.00 p.m. Red blood corpuscles, 5,553,000 per cubic millimeter
3.00 p.m. Red blood corpuscles, 5,284,000 per cubic millimeter

Experiment 43, February 21, 1917

10.00 a.m. Red blood corpuscles, 5,825,000 per cubic millimeter
10.05 a.m. 1 cc. secretin per kilogram of body weight given hypodermatically
10.30 a.m. Red blood corpuscles, 6,522,000 per cubic millimeter
10.55 a.m. Red blood corpuscles, 6,764,000 per cubic millimeter
11.00 a.m. 1 cc. secretin per kilogram of body weight given hypodermatically
11.30 a.m. Red blood corpuscles, 6,004,000 per cubic millimeter
11.55 a.m. Red blood corpuscles, 7,402,000 per cubic millimeter
12.00 noon 1 cc. secretin per kilogram of body weight given hypodermatically
12.30 p.m. Red blood corpuscles, 8,883,000 per cubic millimeter
12.55 p.m. Red blood corpuscles, 6,111,000 per cubic millimeter
1.00 p.m. 1 cc. secretin per kilogram of body weight given hypodermatically
1.30 p.m. Red blood corpuscles, 5,472,000 per cubic millimeter
1.55 p.m. Red blood corpuscles, 7,016,000 per cubic millimeter
2.00 p.m. 1 cc. secretin per kilogram of body weight given hypodermatically
2.30 p.m. Red blood corpuscles, 7,094,000 per cubic millimeter
3.00 p.m. Red blood corpuscles, 8,089,000 per cubic millimeter
4.00 p.m. Red blood corpuscles, 6,912,000 per cubic millimeter

February 22, 1917

10.00 a.m. Red blood corpuscles, 5,446,000 per cubic millimeter

February 23, 1917

10.00 a.m. Red blood corpuscles, 5,296,000 per cubic millimeter

Experiment 44, February 22, 1917

10.00 a.m. Red blood corpuscles, 5,829,000 per cubic millimeter
10.05 a.m. 1 cc. secretin per kilogram of body weight given hypodermatically

February 23, 1917

10.00 a.m. Red blood corpuscles, 5,245,000 per cubic millimeter
10.05 a.m. 1 cc. secretin per kilogram of body weight given hypodermatically

February 24, 1917

10.00 a.m. Red blood corpuscles, 7,710,000 per cubic millimeter
10.05 a.m. 1 cc. secretin per kilogram of body weight given hypodermatically

February 25, 1917

10.00 a.m. Red blood corpuscles, 6,961,000 per cubic millimeter
10.05 a.m. 1 cc. secretin per kilogram of body weight given hypodermatically

February 26, 1917

10.00 a.m. Red blood corpuscles, 5,523,000 per cubic millimeter
10.05 a.m. 1 cc. secretin per kilogram of body weight given hypodermatically

March 1, 1917

10.00 a.m. Red blood corpuscles, 5,975,000 per cubic millimeter

March 4, 1917

10.00 a.m. Red blood corpuscles, 6,218,000 per cubic millimeter

These experiments, numbers 40 to 44 inclusive, show that successive doses of secretin at short intervals are capable of causing a progressive increase in the number of red corpuscles per cubic millimeter of blood, but the increase is not maintained from one dose to the next, so that between the doses there is a diminution from the maximum count resulting from that dose before the next dose exerts an effect. In other words, two doses do not give twice the effect of one dose or three doses three times the effect of one dose. Moreover, when the administration of the secretin is stopped the number of red corpuscles in the circulating blood reverts to normal almost as quickly as after a single dose. In the case of the rabbit which received a daily dose of secretin for five days the increase in the number of erythrocytes per unit volume of blood on the eighth day as compared with the initial count was 146,000, showing that secretin has no ability to produce a permanent increase in the red corpuscle content of the circulating blood of the normal animal.

Three main conclusions are inevitable from the observations that have been recorded: first, secretin, even when injected subcutaneously, is capable of producing an increase in the number of red corpuscles in the circulating blood; second, the increase thus effected is not great as compared with the increase that may be obtained by the action of other agents; third, the length of time that this larger number of red corpuscles persists is comparatively short.

Let us consider briefly the possible therapeutic benefits that may be derived from the exhibition of secretin. If we grant the correctness of the theory of Beveridge and Williams (10) that the red corpuscles constitute one of the chief defensive agencies of the animal organism against the invasion of pathogenic bacteria or the products of such bacteria, then, in order that aid may be given to the establishment of immunity by this means, we must be able in some way to bring about a marked augmentation in the number of red corpuscles and an augmentation that will continue for a time sufficiently long to be of service. We have shown that the most efficient dose of secretin is in the proportion of 1 cc. per kilogram of body weight, which means for the average man 70 cc. of secretin subcutaneously or 38.5 cc. intravenously. Furthermore the effect of this dose disappeared on an average 73.3 minutes after it was given. Moreover, it was not possible to produce a lasting increase in the number of red corpuscles by giving successive doses, either at intervals of one hour, two hours or twenty-four hours. The facts that have been adduced militate against any therapeutic value for secretin but do not detract in the slightest from its physiological significance. On the contrary, they appear to give secretin added importance in the normal organism. It is possible that one of the means by which the normal number of red corpuscles is maintained in the blood stream is the action of secretin.

Naturally the next question that presents itself is: How does secretin produce this increase in the number of the red corpuscles in the circulating blood? This is a question which we are not as yet prepared to answer, but several suggestions can be offered. The first and simplest explanation that presents itself is that secretin exerts a direct stimulating influence upon the red marrow of the bones thus leading to the formation of new cells. Such a conclusion is entirely in accord with the known activities of secretin. If this substance is capable of promoting the activity of the pancreatic cells, of the hepatic cells, and of the cells of the pituitary body, it is entirely reasonable to assume that it may also have the ability to increase the formation of red blood corpuscles by the red marrow of the bones.

A second way in which secretin might bring about an increase in the number of circulating erythrocytes is by causing variations in their unequal distribution. This might be effected by a direct constricting action on the capillaries of some large area, such as the liver, or by an indirect action through stimulation of the adrenals. Lamson (9) has shown that in the cat and dog an increase in the number of red cor-

puscles per unit volume of blood may be obtained by the administration of adrenalin. In the same animals fright raises the number of red corpuscles per unit volume of blood an average of 80 per cent. In both cases there is no increase in the number of erythrocytes if the hepatic artery be ligated. It has been shown by Cannon (11) that fright stimulates the adrenals, and Lamson attributes the presence of a greater number of red corpuscles in the blood stream to a constriction of the capillaries of the liver caused by adrenalin. Mautner and Pick (12) inform us of the presence of an extremely sensitive nervous mechanism in the liver of the dog, reacting to epinephrin by constriction of the capillaries, and the absence of such in the liver of the rabbit, or the presence in this animal of a much less sensitive mechanism. Lamson (13) has shown also that excitement or the intravenous injection of adrenalin causes no polycythemia in rabbits. Therefore, it seems that we can rule out the suggestion that secretin increases the number of red corpuscles in the circulating blood of the rabbit by stimulating the adrenals. As to whether the secretin acts directly to promote capillary constriction or not we have no evidence and do not know of any work that has been reported on the subject.

One other explanation that should be mentioned is the possibility that secretin causes a decrease in plasma volume and thus gives rise to a higher erythrocyte count per cubic millimeter of blood.

The means by which secretin acts to produce an increase in the number of red corpuscles in a unit volume of blood is a question outside of the scope of the present investigation. In undertaking these experiments we were actuated by the desire to know whether secretin increased the number of erythrocytes in the blood stream or not; and, if so, how much of an increase could be hoped for, and how long it would be possible to maintain this increase. These questions have been answered, we believe, and the solution of the mode of action will be found later.

CONCLUSIONS

1. It is possible to produce a considerable increase in the red corpuscle count per cubic millimeter of blood by the administration of secretin even in small doses and by subcutaneous injection.

2. The most efficient dose is 1 cc. of secretin per kilogram of body weight.

3. The increase in the count appears quickly and is very transient.

4. By repeating the dose of secretin at short intervals the increase in the erythrocyte count can be kept up for several hours but drops promptly after the administration of the last dose.

5. The administration of secretin over a period of five days, in daily doses of 1 cc. per kilogram of body weight, has very slight, if any, lasting effect on the red corpuscle count in the normal animal.

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SECRETIN

II. ITS INFLUENCE ON THE NUMBER OF WHITE CORPUSCLES IN THE CIRCULATING BLOOD

BY

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SECRETIN

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In a previous report (1) we have shown that the subcutaneous injection of even a small dose of secretin is able to produce a marked increase in the number of erythrocytes in the circulating blood. In the present report we wish to show that such injections are likewise capable of increasing the number of white corpuscles in the blood stream.

The secretin which we used was in all cases prepared from the intestine of the dog. The mucous membrane was scraped off with a dull knife from the upper half of the small intestine, triturated with 50 cc. of 0.4 per cent hydrochloric acid and after standing for two hours was boiled actively. The preparation was neutralized while boiling and filtered. To it was then added sufficient glacial acetic acid to make 2 per cent by volume and the acid extract evaporated to dryness. We have found that such a preparation retains its activity for at least six months. We obtained about 10 mgm. of this dried acid extract per cubic centimeter of original solution. In all of the present series of experiments such an acid extract was used, a sufficient quantity of the dried preparation being dissolved in normal saline solution as needed to make a solution of the same strength as the original filtrate.

As in our previous experiments rabbits were used exclusively because it has been shown by Lamson (2) that they do not respond to fright, pain, etc., by an increase in the number of erythrocytes in the circulating blood, as do the cat and dog, and we wished to avoid the use of an anaesthetic. Also to exclude the factor of digestion leucocytosis food and water were withheld from the animals during the experiments.

The blood was obtained from the ear of the rabbit with as little manipulation as possible. Specimens were taken simultaneously for counting both white and red corpuscles, 0.5 per cent acetic acid being

used as the diluting fluid for the former and normal saline solution for the latter. The counts were made in the usual manner with the Thoma-Zeiss apparatus.

TABLE 1

Dose: 1 cc. secretin solution per kilogram of body weight

EXPERIMENT NUMBER		INITIAL COUNT	MAXIMUM COUNT	AMOUNT OF INCREASE	PERCENTAGE INCREASE	MAXIMUM IN	DURATION OF EFFECT
						minutes	*minutes*
1	W. B. C.	4,800	7,800	3,000	62.5	30	65
	R. B. C.	(*)					
2	W. B. C.	10,400	13,600	3,200	30.76	30	60
	R. B. C.	4,960,000	5,608,000	648,000	13.06	30	30
3	W. B. C.	9,600	11,250	1,650	17.18	90	90
	R. B. C.	5,331,000	6,240,000	909,000	17.05	90	90
4	W. B. C.	6,200	14,200	8,000	129.03	30	90
	R. B. C.	7,349,000	7,840,000	491,000	6.68	30	30
5	W. B. C.	11,600	16,600	5,000	43.10	60	90
	R. B. C.	6,054,000	7,184,000	1,130,000	18.66	60	60
6	W. B. C.	20,000	34,800	14,800	74.00	60	90
	R. B. C.	5,234,000	7,200,000	1,966,000	37.56	60	90
7	W. B. C.	15,600	11,786†	3,814	24.44	30	60
	R. B. C.	6,427,000	6,631,000	204,000	3.17	90	90
8	W. B. C.	12,654	15,800	3,146	24.86	60	90
	R. B. C.	6,615,000	7,760,000	1,145,000	17.30	60	60
9	W. B. C.	10,900	13,100	2,200	20.18	60	60
	R. B. C.	5,605,000	6,912,000	1,307,000	23.31	60	60
10	W. B. C.	7,400	12,200	4,800	64.86	60	90
	R. B. C.	5,343,000	6,246,000	903,000	16.90	60	60
Averages	W. B. C.	10,915	15,113	4,198	44.2	51	78.5
	R. B. C.	5,879,777	6,846,777	967,000	17.07	50	63.33

* Red corpuscle counts were not made in experiment 1.

† Experiment 7 shows a decrease in the white corpuscle count.

Experiment 5, November 9, 1917

9.50 a.m. White blood corpuscles 11,600 per cubic millimeter. Red blood corpuscles 6,054,000 per cubic millimeter.
9.55 a.m. 1 cc. secretin solution (representing 10 mgm. of dried extract) per kilogram of body weight given hypodermatically.
10.25 a.m. White blood corpuscles 14,400 per cubic millimeter. Red blood corpuscles 6,496,000 per cubic millimeter.
10.55 a.m. White blood corpuscles 16,600 per cubic millimeter. Red blood corpuscles 7,184,000 per cubic millimeter.
11.25 a.m. White blood corpuscles 14,400 per cubic millimeter. Red blood corpuscles 5,984,000 per cubic millimeter.
11.55 a.m. White blood corpuscles 12,400 per cubic millimeter. Red blood corpuscles 5,216,000 per cubic millimeter.
12.25 p.m. White blood corpuscles 8,800 per cubic millimeter. Red blood corpuscles 5,574,000 per cubic millimeter.

We had determined in our previous experiments that 1 cc. of the secretin solution, equivalent to approximately 10 mgm. of the dried extract, per kilogram of body weight was the most efficient dose to produce an increase in the number of erythrocytes per unit volume of blood and that the preparation was effective when injected subcutaneously. Therefore we selected this dose as our starting point and administered it subcutaneously in all cases. Table 1 summarizes the results of ten such experiments, the effect upon both red and white corpuscles being recorded. Following the table is the protocol of a typical experiment of this group.

These experiments show conclusively that not only is secretin solution, when injected subcutaneously, able to produce an increase in the number of erythrocytes in the circulating blood but that it is capable of producing an even greater effect on the number of white blood corpuscles. In addition, however, it shows that the duration of the effect on the number of the corpuscles and the time of appearance of the maximum count are very nearly the same in the two cases—duration of effect on the red blood corpuscles 63.33 minutes, on the white corpuscles 78.5 minutes; maximum count of red blood corpuscles per cubic millimeter in 60 minutes, of white blood corpuscles per cubic millimeter in 51 minutes—the effect being produced quicker in the case of the white corpuscles and persisting longer.

We next sought to determine if the dose of 1 cc. of secretin solution per kilogram of body weight was the most efficient does in the case of the white blood corpuscles as it had been shown to be with regard

to the erythrocytes. To do this we performed four experiments using in each a dose of ½ cc. of secretin solution per kilogram of body weight and four experiments using in each 2 cc. of secretin solution per kilogram of body weight. The results of these experiments are shown in tables 2 and 3 respectively. An experiment typical of each group is also given in detail.

TABLE 2

Dose: 0.5 cc. secretin solution per kilogram of body weight

EXPERIMENT NUMBER		INITIAL COUNT	MAXIMUM COUNT	AMOUNT OF INCREASE	PERCENAAGE INCREASE	MAXIMUM IN	DURATION OF EFFECT
						minutes	*minutes*
11	W. B. C.	16,800	20,600	3,800	22.61	30	60
	R. B. C.	6,961,000	7,671,000	710,000	10.19	30	30
12	W. B. C.	9,200	10,600	1,400	15.21	60	90
	R. B. C.	5,440,000	6,560,000	1,120,000	20.58	60	90
13	W. B. C.	9,200	14,200	5,000	54.34	90	60
	R. B. C.	4,290,000	4,650,000	260,000	8.39	90	60
14	W. B. C.	16,800	18,400	1,600	9.54	60	60
	R. B. C.	6,640,000	6,928,000	288,000	4.33	60	60
Averages	W. B. C.	13,000	15,950	2,950	25.42	60	67.5
	R. B. C.	5,832,750	6,452,250	619,500	10.87	60	60.0

Experiment 11, November 20, 1917

11.05 a.m. White blood corpuscles 16,800 per cubic millimeter. Red blood corpuscles 6,961,000 per cubic millimeter.

11.15 a.m. 0.5 cc. secretin solution (representing 5 mgm. of dried extract) per kilogram of body weight given hypodermatically.

11.45 a.m. White blood corpuscles 20,600 per cubic millimeter. Red blood corpuscles 7,671,000 per cubic millimeter.

12.15 p.m. White blood corpuscles 18.400 per cubic millimeter. Red blood corpuscles 6,624,000 per cubic millimeter.

12.45 p.m. White blood corpuscles 16,000 per cubic millimeter. Red blood corpuscles 6,168,000 per cubic millimeter.

1.15 p.m. White blood corpuscles 14,500 per cubic millimeter. Red blood corpuscles 5,860,000 per cubic millimeter.

TABLE 3

Dose: 2 cc. secretin solution per kilogram of body weight

EXPERIMENT NUMBER		INITIAL COUNT	MAXIMUM COUNT	AMOUNT OF INCREASE	PERCENTAGE INCREASE	MAXIMUM IN	DURATION OF EFFECT
						minutes	*minutes*
17	W. B. C.	11,600	13,000	1,400	12.06	30	90
	R. B. C.	6,576,000	7,263,000	687,000	10.44	30	60
18	W. B. C.	11,700	19,400	7,700	65.81	60	90
	R. B. C.	4,960,000	5,900,000	940,000	18.95	30	90
21	W. B. C.	7,600	7,300*	300	3.94	40	80
	R. B. C.	6,001,000	7,313,000	1,312,000	21.86	30	30
22	W. B. C.	5,400	10,200	4,800	88.88	30	60
	R. B. C.	6,880,000	7,376,000	496,000	7.20	30	60
Averages	W. B. C.	9,075	12,475	3,400	38.21	40	80
	R. B. C.	6,104,250	6,963,000	858,750	14.61	30	60

* Experiment 21 shows a decrease in the white corpuscle count.

Experiment 17, November 27, 1917

11.00 a.m. White blood corpuscles 11,600 per cubic millimeter. Red blood corpuscles 6,576,000 per cubic millimeter.

11.05 a.m. 2 cc. secretin solution (representing 20 mgm. of the dried extract) per kilogram of body weight given hypodermatically.

11.35 a.m. White blood corpuscles 13,000 per cubic millimeter. Red blood corpuscles 7,263,000 per cubic millimeter.

12.05 p.m. White blood corpuscles 12,000 per cubic millimeter. Red blood corpuscles 6,956,000 per cubic millimeter.

12.35 p.m. White blood corpuscles 12,600 per cubic millimeter. Red blood corpuscles 6,118,000 per cubic millimeter.

1.05 p.m. White blood corpuscles 11,500 per cubic millimeter. Red blood corpuscles 6,288,000 per cubic millimeter.

3.05 p.m. White blood corpuscles 8,500 per cubic millimeter. Red blood corpuscles 6,052,000 per cubic millimeter.

A dose of 1 cc. of secretin solution per kilogram of body weight produces an average increase of 44.2 per cent in the number of white corpuscles in 51 minutes, while 0.5 cc. of secretin solution per kilogram produces an increase of only 25.42 per cent in 60 minutes and 2 cc. of secretin solution per kilogram an increase of 38.21 per cent in 40 min-

utes. Therefore the conclusion is justified that 1 cc. of secretin solution per kilogram of body weight is the most efficient dose to increase the number of both white and red corpuscles.

In our previous work on the red blood corpuscles we also found that by repeating the dose of secretin solution at short intervals the increase in the erythrocyte count could be kept up for several hours but dropped promptly after the administration of the last dose. In table 4 the results of four experiments are recorded in each of which 1 cc. of secretin solution per kilogram of body weight was injected subcutaneously at hourly intervals for three doses.

It will be seen that the increase in the white corpuscle count produced by the first dose is partly maintained by the succeeding doses but rises after the administration of the last dose so that at the end of five hours the number of white corpuscles in the blood stream is very decidedly greater than at the beginning of the experiment. In the same table are given the erythrocyte counts in the same experiments which confirm the results that we obtained previously. A comparison of the effects produced when repeated doses of secretin are given at short intervals shows that the total effect on the white corpuscles is more marked and more persistent than is the effect on the erythrocytes.

A similar comparison of the effect of a single dose of secretin solution on the red and white blood corpuscles shows the same relation. In practically all cases the effect on the white corpuscles appears as quickly, or more quickly, than the effect on the erythrocytes and persists for a longer time. Also the average percentage increase in the white corpuscle count per unit volume of blood is in all cases nearly or quite double the percentage increase in the erythrocyte count.

In our previous paper we suggested as the most probable explanation of the increase in the number of erythrocytes in the circulating blood produced by secretin that it is due to a direct stimulating action of the secretin on the red marrow of the bones. We are still inclined to believe that this is the true explanation and further work is being done in an endeavor to determine this. It is conceded that there are two sources for the white blood corpuscles, the bone marrow and the lymphatic tissues in general. It would seem probable because of the much greater effect of secretin on the number of the white corpuscles that it stimulates their production by both the bone marrow and the lymphatic tissues. Further work is also being done along this line.

TABLE 4

Dose: 1 cc. secretin solution per kilogram of body weight at hourly intervals for three doses

EXPERIMENT NUMBER		INITIAL COUNT	FIRST HOUR	SECOND HOUR	THIRD HOUR	FIFTH HOUR	SIXTH HOUR	MAXIMUM COUNT	AMOUNT OF INCREASE	PERCENTAGE INCREASE	MAXIMUM IN
											hours
15	W. B. C.	11,000	13,300	11,600	11,400	14,600	11,800	14,600	3,600	32.72	5
	R. B. C.	4,677,000	4,896,000	6,867,000	5,696,000	5,343,000	5,100,000	5,867,000	1,190,000	25.44	2
16	W. B. C.	9,200	15,300	13,200	12,600	16,200	12,200	16,200	7,000	76.08	5
	R. B. C.	5,280,000	6,608,000	6,768,000	7,160,000	6,076,000	4,708,000	7,160,000	1,880,000	35.60	3
19	W. B. C.	6,800	7,400	7,000	6,800	8,100	7,000	8,100	1,300	19.11	5
	R. B. C.	7,584,000	7,968,000	6,408,000	8,176,000	8,128,000	7,026,000	8,176,000	592,000	7.80	3
20	W. B. C.	6,400	8,800	8,000	6,400	7,800	5,800	8,800	2,400	37.5	1
	R. B. C.	6,288,000	6,672,000	6,608,000	7,488,000	6,886,000	5,876,000	7,488,000	1,200,000	19.08	3
Averages	W. B. C.	8,350	11,200	9,950	9,300	11,675	9,200	11,925	3,575	42.81	4
	R. B. C.	5,957,250	6,536,000	6,412,750	7,130,000	6,603,250	5,677,500	7,172,750	1,215,500	20.40	$2\frac{3}{4}$

CONCLUSIONS

1. It is possible to produce an increase in the number of white corpuscles per cubic millimeter of blood by the administration of secretin, even in small doses and by subcutaneous injection.

2. The most efficient dose is 1 cc. of secretin solution per kilogram of body weight.

3. The increase in the count appears quickly and is very transient, but is greater and more persistent than the increase in the erythrocyte count produced by the same means.

4. By repeating the dose of secretin solution at short intervals the increase in the number of both the erythrocytes and the white corpuscles can be kept up for several hours but is more marked and persists somewhat longer after the last dose in the case of the white corpuscles than in the case of the red corpuscles.

5. It is suggested that the effects described are due to a direct stimulating action of secretin on both the bone marrow and the lymphatic tissues in general.

6. The results of previous experiments on the number of erythrocytes in the circulating blood are confirmed.

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A STUDY OF THE MECHANISM OF RESPIRATION.

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The mechanism of respiration has long been a matter for investigation by physiologists. The muscles which produce the movements of respiration and the nervous control which regulates the activity of these muscles have occasioned much discussion and given rise to many differences of opinion. In an endeavor to gain a clearer conception of the phenomena of respiration and to reach a conclusion that would be satisfactory, to himself at least, the author undertook a series of investigations upon the living human being, the cadaver and animals. The results of these investigations will be given in the following pages.

It is an established fact that inspiration is accomplished by muscular contraction. The muscles involved are voluntary, and their action may be inhibited for a moment or two by an effort of the will. The carbon dioxide soon accumulates in excess, the will is overcome, and respiration begins again.

The muscles that take part in ordinary quiet inspiration are; diaphragm, external intercostals, the intercartilagenous part of the internal intercostals, and the levatores costarum. The action of the external and internal intercostal muscles has given rise to more discussion than that of all the other muscles of the body, and widely differing opinions have been held, and are still held, as to their function. According to some students, notably Haller, Borelli and Cuvier, both the external and internal intercostal muscles are inspiratory, while the opposite opinion, that they are both expiratory, was maintained by Vesalius and Beau. Spigelius believed the external intercostal muscles to be inspiratory and the internal intercostals to be expiratory; but the contrary opinion was held by Bartholinus, who thought the external intercostals are expiratory and the internal are inspiratory. These two groups of muscles were credited with activity in both inspiration and expiration by Magendie and Mayow; while by others, notably Arantius and Cruveilhier, their importance as muscles was rejected and they were said to act only as part of the resisting wall of the thorax filling in the space between the ribs. At the present time the weight of evidence is in favor of regarding the external intercostal muscles and the intercartilagenous part of the internal intercostal muscles as muscles of inspiration. The author ventures to add his testimony in support of this view. With regard to the function of the interosseous part of the internal intercostals more will be said later.

In addition to the muscles of inspiration that have been named, there are the extraordinary muscles of inspiration, which bring about the movements of forced inspiration. These muscles are the sterno-cleido-mastoids, scaleni, trapezii, pectorales major and minor, rhomboids, serrati postici superiores, serratus magnus, levatores costarum longi et breves, and some of the muscles of the face, palate and larynx.

Ordinary quiet expiration is effected by the relaxation of the muscles of quiet inspiration. When the muscles of inspiration contract they enlarge the thorax in every direction. The contraction of the diaphragm causes it to descend and enlarge the

chest cavity in the vertical diameter. The action of the other muscles of inspiration is to elevate the ribs. Because of the shape, position and attachments of the ribs, to elevate them necessitates their rotation outward at the sides of the chest and the carrying forward of their anterior ends with the attached sternum. Elevation of the ribs therefore causes enlargement of the chest in the transverse and antero-posterior diameters. As there is always a negative pressure between the chest walls and the lungs, the latter are held in apposition with the walls of the thorax, and when the chest enlarges by the outward movement of its walls the lungs are correspondingly enlarged. This causes a fall of air pressure within the lungs below the pressure of the outside atmosphere, and air is driven into the lungs until the pressure within them equals that outside the body. This constitutes inspiration.

Expiration is accomplished by the relaxation of the muscles of inspiration. Because of their elasticity these muscles return to their position when the stimulus to contract is removed. The diaphragm relaxes and rises into the chest cavity. The ribs and sternum possess weight, and their weight was lifted by the contraction of the muscles of inspiration. When those muscles relax, the weight of the ribs and sternum will cause them to fall. If the elevation of these parts causes an increase in the transverse and antero-posterior diameters of the thorax, their fall, or depression, will cause a decrease in the same diameters. This weight, together with the elasticity of the muscles, aided by the elasticity of the lungs that have been stretched during inspiration, is sufficient to press upon the contents of the lungs and raise the air pressure within them above that of the outside world. As a result, a quantity of air approximately equal to that which entered during inspiration is forced out and the air pressure in the lungs becomes the same as the external atmospheric pressure. This constitutes expiration.

It will be observed that no muscular contraction is necessary to effect expiration. The muscles that are usually designated as muscles of ordinary expiration are really muscles of extra-ordinary expiration. These are the interosseous part of the internal intercostals, the triangularis sterni and the infra-costales. During inspiration these muscles are stretched, and when the stretching force is removed they return to their resting position because of their elasticity. By their elastic shortening from an extended condition they aid expiration, but they do not aid quiet expiration by an active contraction. During forced expiration these muscles do contract in association with the

other muscles of extraordinary expiration, viz., the oblique and transverse muscles of the abdomen, quadratus lumborum and posterior inferior serratus.

The mechanical arrangement invented by Bernouilli and familiar to all physiologists that is used to imitate and demonstrate the action of the external and internal intercostals is true in its action, but the interpretation is faulty. The device to which I refer consists of two parallel bars, representing the ribs, and two vertical rods, one long and one short, representing respectively the vertebral column and the sternum. Place the parallel bars in an oblique or slanting position with the sternal end lower than the vertebral end to represent the ribs at rest. Now attach two rubber bands to represent the external and internal intercostal muscles. Shortening of the external intercostal band elevates the bars—it is inspiratory. At the same time the internal intercostal band is stretched. When the stretching force is removed it shortens because of its elasticity and depresses the bars—it is expiratory. That is true, but in order to act as a muscle of expiration it must shorten beyond its resting position and depress the bars, or ribs, still more, and that is what happens in forced expiration. When the muscles of inspiration contract, the internal intercostal muscles are extended. An extended muscle returns to its resting position when the stretching force is removed. The muscles of inspiration relax, and the internal intercostals, because of their elasticity, return to their resting position, the ribs fall, and expiration is completed. As soon as the internal intercostal muscles contract they pull the ribs down below their normal position at the end of expiration; in other words, expiration becomes forced or extraordinary. An error made in using the invention of Bernouilli is to begin with the bars horizontal instead of slanting downward and forward.

In order to determine positively whether the interosseous part of the internal intercostal muscles contracted in expiration, a series of one hundred determinations of the presence or absence of an action current during quiet expiration was made. A similar number of determinations with regard to an action current in the external intercostal muscles and in the intercartilagenous portion of the internal intercostals during expiration was made.

Reference to the tabulated report of the results of these studies, Table 1, shows that an action current was present in the interosseous part of the internal intercostal muscles twenty-two times and absent seventy-eight times. The external intercostals showed an action current only three times and

the intercartilagenous portion of the internal intercostals seven times. The evidence seems conclusive that these muscles do not take part in ordinary quiet expiration. The fact that the interossei showed an action current so often as they did, twenty-two times, was probably due to the fact that the animal was being operated upon and respiration was somewhat exaggerated at times, though every precaution was taken to insure respiratory movements as nearly normal as possible.

	Internal Intercostals (Interossei)	External Intercostals	Internal Intercostals (Intercartilagenei)		Internal Intercostals (Interossei)	External Intercostals	Internal Intercostals (Intercartilagenei)		Internal Intercostals (Interossei)	External Intercostals	Internal Intercostals (Intercartilagenei)
1				35				69	*		
2				36	*			70			
3				37				71			*
4			*	38				72			
5	*			39				73			
6				40	*			74			
7				41	*			75			
8	*			42				76			
9	*			43				77	*		*
10				44				78			
11				45				79			
12	*			46				80			
13				47	*			81			
14		*	*	48			*	82			
15				49		*		83			
16	*			50				84			
17	*			51		*	*	85			
18	*			52	*			86			*
19				53				87			
20				54				88	*		
21				55				89			
22				56				90			
23				57				91			
24	*			58				92			
25				59	*			93			
26	*			60				94			
27				61	*			95			
28				62				96			
29				63				97			
30				64				98			
31				65	*			99			
32				66				100			
33				67	*						
34				68	*						

TABLE 1.

Electrical Condition of the Internal Intercostal Muscles (Interosseous Portion), External Intercostal Muscles, and Internal Intercostal Muscles (Intercartilagenous Portion) during Quiet Expiration.

* Indicates presence of an action current.

Observations were next made upon the external and internal intercostal muscles during quiet inspiration. Here the results

were most interesting. The external intercostals showed an action current in every case in one hundred readings. The interosseous portion of the internal intercostals showed an action current eleven times in one hundred determinations. These investigations point to the external intercostals as muscles of inspiration and the internal intercostals as not being active during inspiration. While no special attention was paid to the intercartilagenei during inspiration, it seems reasonable to believe from the results obtained during expiration that in function they are associated with the external intercostals.

Our next procedure was to administer caffeine in order to stimulate the respiratory centre and bring about forced respiration. The electrical condition of the interossei and external intercostals was again noted, and the former showed an action current during expiration in one hundred observations; while the latter showed the presence of the current during inspiration, but only eight times during expiration.

The conclusion the author draws from these experiments is, that the external intercostal muscles and the intercartilagenous portion of the internal intercostals are muscles of inspiration, and that the interosseous portion of the internal intercostals is not active during quiet expiration but does take part in extraordinary expiration.

Having satisfied ourselves as to the actions of the muscles of inspiration and expiration, the next problem to be studied was the action of the respiratory centre. Another series of one hundred experiments was performed during which the electrical condition of the vagus nerve was observed. These experiments showed that when air enters the lungs an action current is produced in the vagus. When the air leaves the lungs there is usually no action current present (Table 2). In a few cases—eleven—there was a negative variation; in six cases there was a pronounced positive variation lasting until the next inspiration took place. Here the results point to an impulse generated in the vagus by distension of the lungs during inspiration.

In the light of these experiments the author concludes that the respiratory centre is essentially inspiratory in its activity. This centre is composed of nerve cells whose normal stimulus is carbon dioxide. As a result of the functional activity of the cells and tissues of the body, carbon dioxide is produced constantly. This carbon dioxide is taken from the cells by the blood and carried through the circulation. It comes in contact with the cells composing the respiratory centre, stimulates them, and they send out motor impulses to the muscles of

inspiration. Those muscles contract, the thoracic cavity is enlarged, the lungs are distended, and air is forced into the

1	0	21	—	41	0	61	0	81	0
2	0	22	0	42	0	62	0	82	0
3	0	23	—	43	0	63	0	83	0
4	0	24	0	44	0	64	0	84	+
5	0	25	0	45	0	65	0	84	+
6	0	26	0	46	0	66	0	86	0
7	—	27	+	47	0	67	0	87	0
8	—	28	0	48	—	68	0	88	0
9	—	29	0	49	—	69	0	89	0
10	0	30	0	50	0	70	0	90	0
11	0	31	0	51	0	71	0	91	0
12	0	32	0	52	0	72	0	92	0
13	+	33	0	53	0	73	0	93	+
14	—	34	0	54	0	74	0	94	0
15	0	35	0	55	0	75	0	95	0
16	0	36	0	56	+	76	0	96	0
17	0	37	0	57	0	77	—	97	0
18	0	38	0	58	0	78	0	98	0
19	0	39	0	59	0	79	0	99	0
20	—	40	—	60	0	80	0	100	0

TABLE 2.

Electrical Condition of Vagus Nerve During Expiration. "0" indicates absence of electrical change; — indicates a negative variation; + indicates a positive variation.

lungs, constituting inspiration. As a result of the distension of the lungs during inspiration, an impulse is aroused in the sensory fibres of the vagus nerve distributed to the lungs. This impulse travels to the central nervous system and inhibits the respiratory centre. The lungs having been filled with air, the respiratory centre must be informed of that fact so it may cease to command contraction of the muscles of inspiration, and that information is furnished through the vagus by the impulse generated in its sensory fibres by the stretching of the lungs. The respiratory centre being inhibited, it allows the inspiratory muscles to relax, and air is forced out of the lungs in the manner previously described. As the lungs become smaller the sensory fibres of the vagus nerve return to a condition of rest and the respiratory centre is again free to respond to the presence of carbon dioxide. As a result another inspiration is initiated and the preceding cycle of events is repeated.

During forced, or extraordinary, expiration the muscles of expiration are brought into play. They may contract under the influence of the will to produce a more forcible expiration than usual, or they may be excited to activity by the accumulation of large amounts of carbon dioxide. During ordinary quiet breathing it is possible at any time to make a strong expiration by the exercise of the will and commanding the muscles of expiration to contract. When the activity of the cells is increased, as in muscular exercise, there is an increased production of carbon dioxide which stimulates the respiratory

centre and causes deeper inspirations. At the same time this carbon dioxide, if in large amount, stimulates the expiratory portion of the respiratory centre, and it sends out impulses to the muscles of expiration, thus bringing about forced expiration.

In summing up, we conclude that in quiet breathing we must regard inspiration as active, due to muscular contraction, and expiration as passive, due to the relaxation of the muscles of inspiration and the return of the parts involved to their resting condition. The respiratory centre, situated in the medulla oblongata, we believe to be composed of inspiratory and expiratory portions which possess different degrees of reaction to carbon dioxide, the inspiratory portion responding to a smaller proportion of carbon dioxide in the blood than is required to arouse to activity the cells composing the expiratory portion. Therefore the centre tends constantly to send out inspiratory impulses, and its activity is inhibited by impulses coming to it from the lungs through the sensory fibres of the vagus nerve, these inhibitory impulses coming from the lungs being generated in the vagus by the distension of the lungs during inspiration.

In presenting the above conclusions the author realizes full well the difficulties and liability to error attending such experiments. The results are published, not with the idea that they are unquestionably accurate and that they represent conditions that will always be found at corresponding times in all animals, but in the hope that they will add a little to our knowledge of an imperfectly understood part of physiology. In carrying on the investigations the living human subject was employed for the purpose of observing the respiratory movements during repose, exercise and after exercise. The cadaver was used for an anatomical study of the parts involved. For the animal experiments dogs were used. Two or three hours before the animal was to be experimented upon a subcutaneous injection of morphine sulphate was given, usually 0.2 G. At the time of operation, to produce anæsthesia, a solution of chloretone in alcohol diluted with an equal quantity of water was administered through a stomach tube. The dose of chloretone was about 3 G., varying slightly with the weight of the dog. In a few cases moderate ether anæsthesia was employed and in others paraldehyde, in the proportion of 1.5 c. c. per kilogram of body weight, given by the stomach tube. No appreciable differences in the results obtained could be traced to the influence of the various anæsthetics. Careful dissections were made with as little exposure and injury of the tissues as possible. A capillary electrometer was employed to determine the electrical condition. These experiments were made before the judicial decision in Pennsylvania relative to animal experimentation.

TWO SUGGESTIONS OF APPARATUS FOR THE TEACHING LABORATORY

1. A Device for the Determination of Time of Muscular Contraction and Relaxation.
2. An Automatic Key.

By

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TWO SUGGESTIONS OF APPARATUS FOR THE TEACHING LABORATORY*

1. A Device for the Determination of Time of Muscular Contraction and Relaxation. 2. An Automatic Key.

By Ardrey W. Downs, M.D., and George Hays, M.D., Montreal, Canada

THE first apparatus described in this paper (Fig. 1) is a simple contrivance designed to give a more accurate measurement of the time occupied by the contraction and by the relaxation of a muscle than does the mechanism usually employed. It consists of a rectangular piece of metal 7 cm. long and 1½ cm. square placed vertically with a metal rod 15 cm. long and 7 mm. in diameter

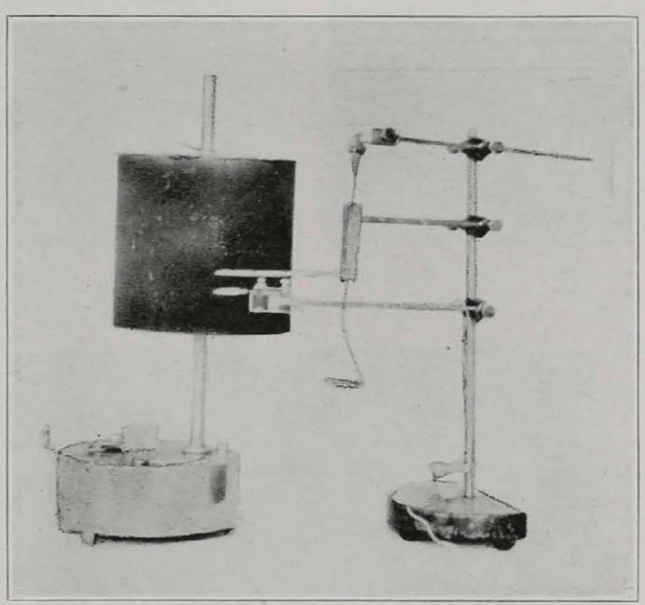

Fig. 1.

attached at right angles near one end to serve as a support. This rod may be clamped to the ordinary stand. Through the center of the vertical block from end to end is drilled a round hole eight millimeters in diameter, and in this a small metal disc, or piston, is accurately fitted. To the upper surface of this disc is fastened a wire for the attachment of the muscle, and to its lower surface is fastened another wire for the suspension of a scale pan. A writing lever is secured to the side of the disc and allowed to project through a slot cut through the cylinder wall from top to bottom. This permits the disc to be moved up and down in its containing cylinder. The muscle may be held in any suitable clamp, in this case a muscle clamp of the type made by the Harvard Apparatus Company.

The muscle lever ordinarily used to record a muscle curve is the radius of a circle and when lifted by the contracting muscle its writing point describes the

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arc of a circle. It is obvious that in making a tracing of a muscle curve on a revolving drum the apex of the curve is moved backward, that is, away from the point at which the curve began, because of two factors; the movement of the surface of the drum past the writing point and the arc drawn by the muscle lever when elevated. The second of these factors adds to the apparent length of the period of contraction an appreciable length of time due entirely to

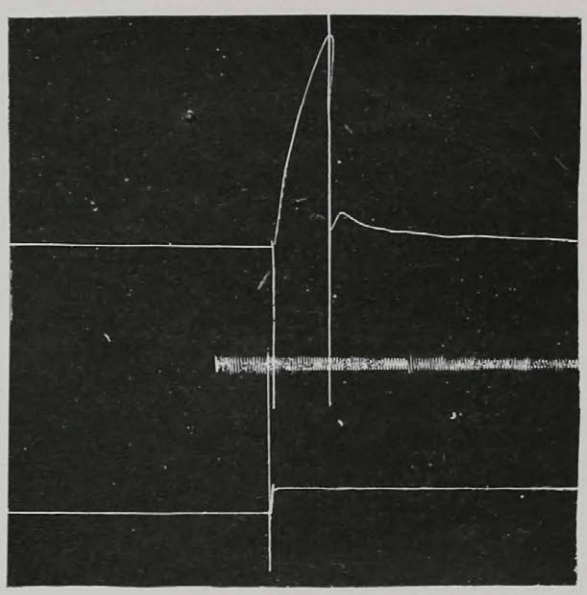

Fig. 2-*A*.

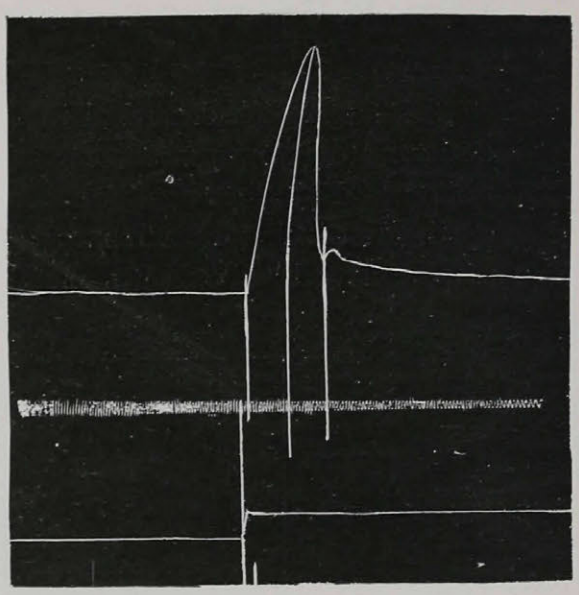

Fig. 2-*B*.

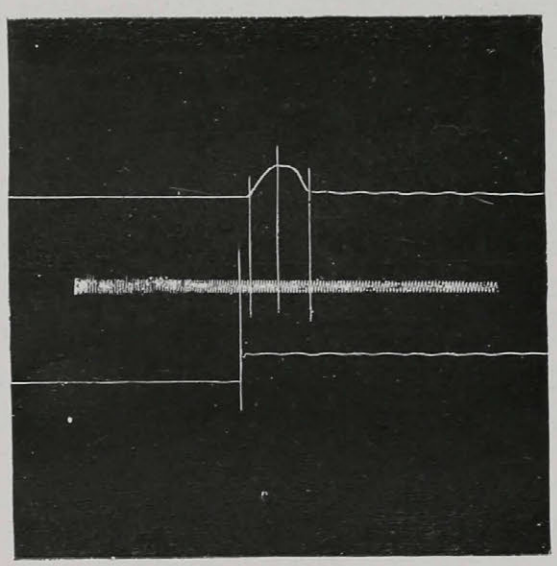

Fig. 3.

the method of operation of the apparatus. In some cases the arc formed by the writing point is so great as to inscribe a muscle curve in which the apex is behind the point where the lever returns to the base line; i. e., the point indicating the termination of the period of relaxation. In such a case the error is obvious, but in every muscle curve drawn by this method there is an error due to the factor described. It is claimed that this error may be eliminated by allowing the writing lever to inscribe its arc from the apex of the

muscle curve to the abscissa line with the drum stationary, and computing the time from the beginning of the curve to the intersection of this arc with the abscissa line as the true period of contraction. The objections to this method are that it is inconvenient, is apt to be inaccurate, and is, therefore, unscientific.

Two muscle curves exemplifying the foregoing statements are shown in Fig. 2. In Fig. 2*A* is seen a muscle curve ruled with vertical lines from the beginning of the curve, the apex, and the point where the lever returns to the base line, to the time record. It is unnecessary to point out the inaccuracy. In Fig. 2*B* a similar curve is corrected by drawing the arc from apex to base line and then ruling the usual vertical lines. This curve still fails to show the proper relationship between time of contraction and time of relaxation.

In Fig. 3 is shown a muscle curve inscribed by our apparatus and ruled

Fig. 4.—One-half actual size.

in the usual manner. In using this device inaccuracies such as may occur by the method just described are impossible. The writing point can move only in a vertical direction and, therefore, the section of the drum that passes the writing point during the contraction and also during the relaxation of the muscle must represent only the time during which the lever was being raised by the contraction of the muscle or allowed to fall by its relaxation. There is, of course, no magnification as with the usual muscle lever, but the ordinary muscle (in this case the gastrocnemius of a frog) with proper adjustment of load and strength of stimulus will give a contraction curve sufficiently high.

The second suggestion that we wish to make is a simple key which can be

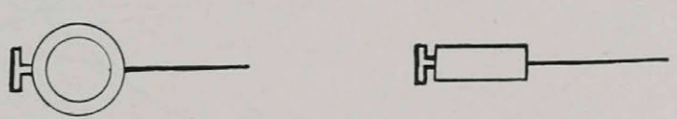

Fig. 5.—One-half actual size.

easily made and attached to the Harvard kymograph. It is so constructed that the primary electric current is broken at any one desired point on the circumference of the drum and is always broken at exactly the same point with each succeeding revolution. Our object in making this key was to secure an arrangement that could be made easily and cheaply, so that it would be suitable for use in a teaching laboratory, which would enable the student to obtain a break shock at identically the same point every time the drum revolved. It is unnecessary to point out the advantages of such a device in recording a series of contractions of a voluntary muscle to show the changes in the contraction curve as the muscle becomes fatigued, or in recording the effect of load upon the contraction of such a muscle. It is not suggested that this key is any better than, or even so good as, automatic keys in use in various laboratories; but

it is intended to offer something which may be helpful to those who are using the Harvard kymograph and have felt, as have the authors, the need of some such attachment.

As may be seen from Fig. 4 the apparatus consists of a hard rubber base 4½ cm. long and 2 cm. wide which is attached to the upper surface of the base of the kymograph by two screws passing through the vulcanite block at two corners and entering holes drilled through the metal plate forming the upper surface of the kymograph base. In this hard rubber block two binding posts are fastened for the attachment of wires of the primary circuit. One binding post is shorter than the other and carries a metal bar which can be allowed to rest on the taller binding post and which can be swung upward and backward away from the post on which it rests. To accomplish this it is hinged loosely

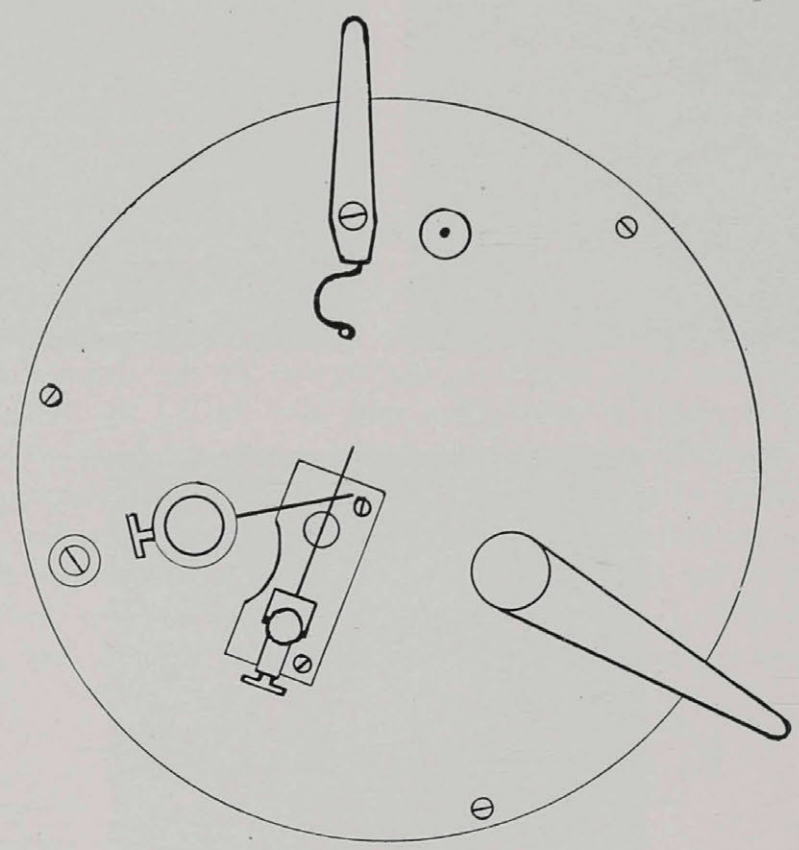

Fig. 6.—One-half actual size.

by a horizontal rod passing through a hole drilled through the shorter of the two posts at right angles to the line joining the binding posts. The only portion of the device remaining to be described consists of a ring (Fig. 5) which encircles the brass sleeve that supports the drum. This ring is held in position by a set screw and carries a rod three centimeters long projecting horizontally. This rod acts as a striker, raises the bridge connecting the two binding posts and carries it onward until it passes beyond the vertical position and drops down and away from the first post. As soon as the bridge is raised the primary circuit is broken and before the drum has completed its revolution ample time is afforded the experimenter to close the short-circuiting key, make the current in the primary circuit by swinging the bridge over into position so as to connect

the two binding posts, and open the short-circuiting key. When this is done the next revolution of the drum gives a break shock at exactly the same point as before. Or, if more convenient, the operator may wait until the curve has been recorded, stop the drum, and reset the key. One great advantage possessed by such a key as we have described is that after the contact has been broken it makes no difference how often the drum revolves there can not possibly be any further stimulation of the preparation until the experimenter closes the key. In our experience this last feature is particularly valuable in the case of students.

Fig. 6 shows the position of the key upon the upper surface of the base of the kymograph.

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THE GENESIS OF THE HEART BEAT.

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THE reason why the heart muscle contracts is of great importance to us, not only as physiologists, but as practical physicians. The highest aim of the medical profession is to cure disease, or, better still, to prevent disease. In addition to the various lesions of the heart itself, the condition of that organ is of the utmost importance in every variation of the body from the normal state. Whether the condition present be acute or chronic, medical or surgical, we always investigate the heart and feel better satisfied if it is in good working order. When such is not the case one of our aims is to give such treatment as will restore normal activity, for it is by means of the heart that circulation of the blood is maintained, nutritive material carried to all the tissues of the body, and waste matters removed. When the heart is not adequately performing its function it inevitably follows that the tissues do not receive the pabulum they need to maintain them in a state of health, and at the same time the waste products of metabolism accumulate and exert a deleterious influence on the tissue-cells.

The importance of normal heart action being recognized, it follows that in order rationally to prescribe treatment with the view of restoring a disordered heart to normal we must know what the factors are that cause the heart muscle to contract in its characteristic rhythmical manner.

The cause of the heart beat has naturally constituted one of the fundamental objects of physiological inquiry, and different views have been held with each new discovery. The modern conception of the cause of the contraction of the cardiac muscle is to be attributed to Haller. In 1757 this observer first taught that the activity of the heart is not dependent on its connections with the central nervous system. Cardiac activity is controlled and influenced constantly by the central nervous system, but he established beyond question the important point that the heart continues to beat after all nervous connections have been severed. Haller, therefore, concluded that the central nervous system regulates the activity of the heart, but has nothing to do with the cause of the rhythmical contractions. He designated the heart as an automatic organ.

Remak, in 1848, discovered nerve-cells in the frog's heart and attributed the beat to them. Nerve-cells were then found to be present in the substance

of the heart tissue of all vertebrates, and during the middle and latter part of the nineteenth century the automaticity of the heart was believed to be due to the properties of its contained nerve-cells. This constitutes the "neurogenic theory of the heart beat." In the latter part of the same century the opposite view became the prevalent one. This is known as the "myogenic theory of the heart beat," and rests on the belief that the muscular tissue of the heart possesses automatic rhythmical contractility. With either of these theories we still have to solve the deeper problem of the automaticity itself,—the cause or causes of the rhythmical excitation; whether it occurs primarily in the muscle-cells or nerve-cells.

The investigations of William Harvey (1628) form the dividing line between the ancient and modern views of the heart beat. Hippocrates and Galen believed diastole to be the active part of the beat. Harvey proved that the active movement of the heart is contraction during systole, and that the contraction is not dependent upon any external influence. Harvey was closely followed by Willis, who propounded the neurogenic theory. He taught that the cerebellum controls the activity of the involuntary organs. With Haller (1757), the myogenic theory came into prominence for the second time. His belief was that the contraction is due to the inherent irritability of the muscle and that it is excited by the venous blood. The work of Remak upon the ganglia of the heart has been mentioned. Experiments on frogs and tortoises reported by Gaskell (1881) support the myogenic theory and give evidence that the intrinsic ganglia of the heart form part of the cardiac inhibitory apparatus.

The neurogenic theory attributed the origin of the excitation of each beat to the nerve-cells located at the junction of the great veins with the right auricle. This was considered the chief automatic motor center of the heart. From this center the impulse was believed to be transmitted to the subordinate nerve-centers in various parts of the heart. The myogenic theory is chiefly the outcome of the work of Gaskell and Engelmann, and rests on the belief that the heart muscle itself possesses the property of automatic rhythmical contraction. This property is most highly developed at the venous end of the heart and is transmitted by the muscle-fibers. One of Engelmann's experiments was to cut the ventricle in zigzag fashion, leaving irregular strips connected by narrow bridges. On stimulating at one end a wave of contraction is started which propagates itself over all the pieces. If a ligature be tied tightly at the junction of the great veins with the heart, the heart will stop beating. This is known as the first ligature of Stannius. Now, after the heart has ceased beating, if the ventricle be irritated a reversed rhythm will result, *i.e.*, the ventricle will contract first and then the auricles, instead of the normal sequence of auricular contraction followed by ventricular. In such an experiment the contraction is probably carried from the muscle of the ventricle to the auricles by means of the band of muscle-tissue that connects auricles and ventricles. With our present knowledge of the nervous system we cannot conceive of definitely arranged nerve-cells with their fibers conveying impulses in opposite directions.

Isolated strips of heart muscle will contract rhythmically, and it is very unlikely that each of these pieces of muscle, irregularly cut from the heart, should contain its own group of motor nerve-cells capable of sending out rhythmical impulses. Moreover, pieces of muscle cut from the apex of the heart, where ganglion-cells cannot be shown to exist, will exhibit rhythmical contractions. As the part removed contains no nerve-cells the contractions can arise only in the muscular tissue. Furthermore, the embryonic heart muscle has rhythmical contractile power, for the cardiac rhythm is established before the ganglion-cells grow into the heart.

We are prone to regard the heart solely as a muscle and to attempt to explain its activity by comparison with the other types of muscle with which we are familiar. In so doing we lose sight of the fact that the heart is an organ with a definite function to perform. Every tissue and organ of the body is the result of proliferation of the original germ-cells, with differentiation and specialization of those cells so that the mature cells are capable of performing a definite kind of work in the economy. Just as the liver or kidney is an organ composed of cells specialized to perform certain functions, so is the heart an organ composed of cells whose duty it is to contract rhythmically and force the blood through the blood-vessels. These organs as they exist in the mammalia are the result of development through many generations, each group of cells inheriting its tendency to perform a certain function.

Romberg isolated portions of the rabbit's heart devoid of ganglia by crushing, but maintained the circulation, and these pieces pulsated for hours. Excision of the entire septum of the frog's heart, including Remak's ganglion, has no disturbing effect on the beat.

The heart beat, however, is undoubtedly under nervous control, and this control is exercised in an inhibitory manner. Without the control of the nervous system the heart would beat more rapidly and more forcibly than necessary. This inhibitory influence is exerted through the pneumogastric nerve. The cardiac branch of the pneumogastric nerve terminates in relation with ganglion-cells located at the junction of the great veins with the right auricle. From these nerve-cells fibers pass to the heart muscle. When a ligature is tied at the position of these ganglion-cells the heart stops beating (first ligature of Stannius). Cardiac activity ceases because the wave of contraction originating in the great veins is cut off from the heart and because the inhibitory cells are mechanically stimulated. If another ligature be tied around the auriculoventricular groove the ventricle contracts again (second ligature of Stannius). The ventricle beats because the inhibitory impulses are cut off and because the muscle is mechanically stimulated. Constant stimulation of heart muscle causes rhythmic contractions.

The heart pulsates when excised. This is not due to the blood in the cavities of the heart, for the latter contracts when its cavities are empty. It is not due to contact of the air, for the heart pulsates in a vacuum. It is not due to irritation received from the nervous system, for the heart is not connected with the nervous system, and it is not due to the ganglia, for portions without ganglia will pulsate. The muscle is irritable, and for this irritability nutrition

is necessary. Erichsen exposed the heart in warm-blooded animals, instituted artificial respiration, and ligated the coronary arteries. In 6 experiments the heart ceased beating in twenty-three and one-half minutes. Activity was restored by removing the ligatures from the coronary arteries and allowing the blood to circulate in the substance of the heart.

The demonstration that the nerve-cells are not essential to contraction places us one step nearer the true cause of contraction. The heart is automatic, *i.e.,* the stimuli which excite it to activity originate within the heart itself. This agency is called the "inner stimulus," and in attempting to discover the nature of this stimulus particular attention has been drawn to the influence of the chlorides of sodium, calcium, and potassium. These salts are brought to the heart muscle by the blood and must be present in certain definite proportions. The sodium chloride maintains the normal osmotic pressure between the muscle-fibers and the surrounding lymph. The calcium chloride acts to maintain normal contractility and irritability of the muscle, while the potassium chloride promotes relaxation of the muscle and regulates the rate and force of the beat.

In the light of our present knowledge we conclude that the heart is an organ with a definite function to fulfill and possessing an inherited tendency to contract rhythmically in order to perform that function, that its activity is regulated by the nervous system, and that its continued action is dependent on the maintenance of its nutrition together with the supplying to it of certain inorganic salts in proper proportions.

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EFFECT OF ALCOHOL ON THE HEART MUSCLE.

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THE experiments here recorded were undertaken to determine the exact effect, so far as possible, of alcohol in various known strengths when brought directly in contact with the heart muscle of the living animal. The conclusions drawn are based on the average result for each strength of alcohol used, and the tracings introduced for the purpose of illustration were selected as being those most nearly typical in each case. Eight strengths of alcohol were used: 1 per cent., 2 per cent., 5 per cent., 10 per cent., 20 per cent., 30 per cent., 40 per cent., and 50 per cent. The method employed was to record the normal heart beat of a frog, and then to apply slowly, by means of a pipette, 30 c.c. of the dilute alcohol. Graphic records were made at intervals of one minute after beginning the application of the alcohol, two minutes, five minutes, ten minutes, fifteen minutes, and thirty minutes.

When 1 per cent. alcohol was applied there was at first a slight increase in the rate of the heart beat, accompanied by a slight decrease in the force. At the expiration of two minutes both rate and force were increased. It was also noted that each pulsation of the great veins at the base of the heart and contraction of the auricles became much more pronounced and of longer duration. When five minutes had elapsed the heart beats were decidedly weaker, and the changes observed in the contractions of the auricles and great veins had disappeared. The heart action became gradually weaker, and in eighty-five minutes contraction ceased.

Two per cent. alcohol produced effects similar to those caused by 1 per cent. alcohol. During the first two minutes there was slight acceleration of rate with increased force, and the same changes in the contraction of the auricles and great veins. Following this there was rapid decrease in strength until activity ceased.

Five per cent. alcohol caused a gradual, uniformly progressive decrease in rate and strength of the contractions. The effect was decidedly perceptible five minutes after beginning the application of the alcohol. The average time at which contraction ceased was sixty-three minutes.

Ten per cent. alcohol caused a marked slowing of the rate of contraction during the first five minutes. When ten minutes had elapsed it was seen that

1 Bassler: "A New Method of Treatment for Chronic Intestinal Putrefactions by Means of Rectal Instillations of Autogenous Bacteria and Strains of Human Bacillus Coli Communis," *Medical Record*, September 24, 1910.

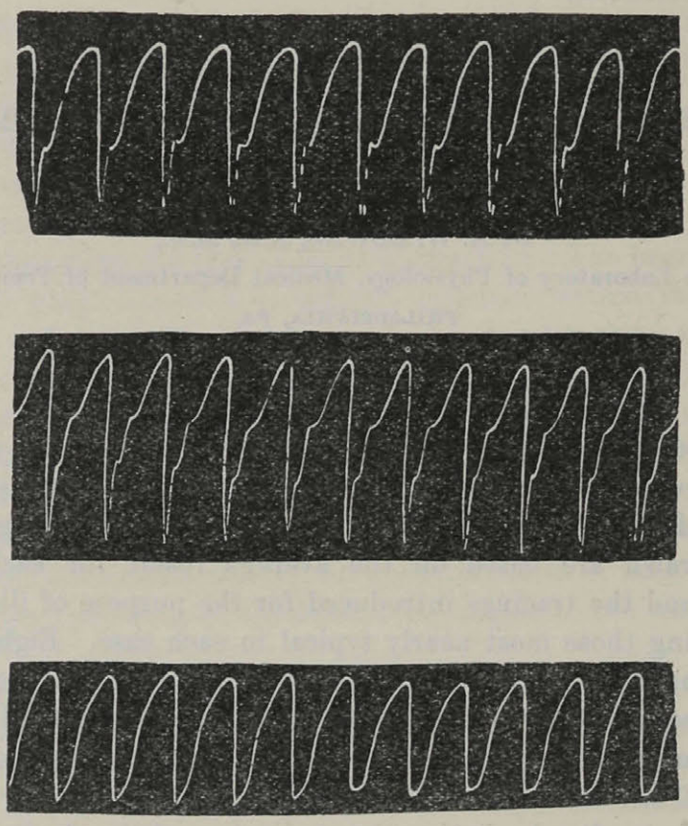

Fig. 1.—Effect of 1 per cent. alcohol on the frog's heart.

the ventricular contraction was much longer in reaching its maximum, and the strength of the beat was much less. The interval between contractions was not appreciably affected. The heart stopped beating in fifty minutes.

The first effect of the application of 20 per cent. alcohol was to cause a sudden and startling decrease in the strength of the contraction of the heart muscle. This was followed by slight recovery during the first five minutes.

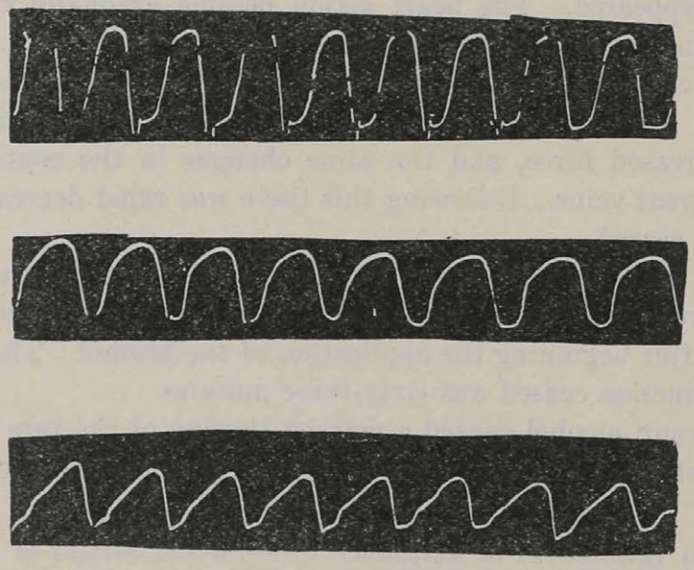

Fig 2.—Effect of 10 per cent. alcohol on the frog's heart.

When ten minutes had elapsed the depressing effect was again evident, and the muscle was incapable of further activity at the expiration of thirty-five minutes.

When alcohol having a strength of 30 per cent. was applied the heart action became slower, and after about one minute the beats became not only weaker, but very irregular. There would be a pause of five or ten seconds, followed by from one to a dozen beats and then another pause, which would be again followed by a varying number of beats. This would continue with longer pauses and the beats growing progressively weaker, until contraction ceased. The average time in which it stopped was twenty minutes.

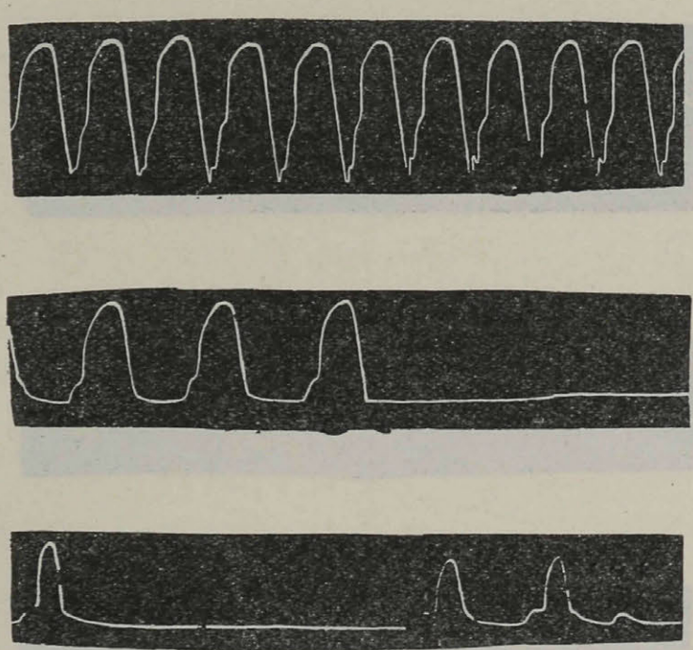

Fig. 3.—Effect of 30 per cent. alcohol on the frog's heart.

Forty per cent. alcohol caused a rapidly progressing decrease in the rate and force of the heart beat, with long periods of inactivity and complete cessation in eight minutes.

The heart action ceased abruptly when 50 per cent. alcohol was applied. After an interval of seven to ten seconds there was a contraction or two, followed by another period of rest, and then a few weak contractions at irregular intervals. Two minutes and fifty seconds was the average time after the application of the alcohol when activity ceased. It was noted that whenever alcohol having a strength of 50 per cent. was applied to the normally contracting heart muscle the contraction stopped abruptly with the heart in a state of diastole. Several seconds always elapsed before contraction was resumed, and then it was invariably much weaker than normal.

Having thus briefly described the effects observed when alcohol of various strengths is applied to the heart muscle of the frog, we now wish to see what conclusions may be drawn from the facts recorded. First of all it is well to remember that the cardiac muscle is different from all other muscles in the

body. It is not under the control of the will, and has a rhythmic activity that differs greatly from the activity of what we commonly call involuntary muscle. The characteristics that are peculiar to the heart muscle of frogs are also characteristics of the heart muscle of the mammalia. For this reason the action of a drug on the frog's heart will indicate its action on the heart of the human being.

In every case the frogs used for experimental purposes were kept under observation for two hours or more, and in none was there any return of heart action. It will be noticed that, with the exception of 1 and 2 per cent. alcohol, there was always a depression of cardiac activity when the alcohol was applied.

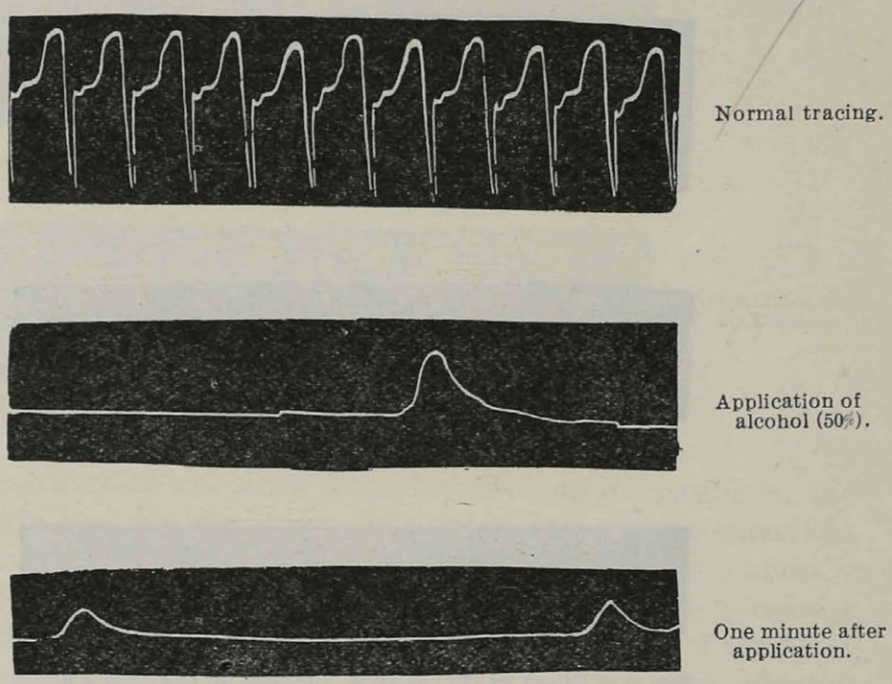

Fig. 4.—Effect of 50 per cent. alcohol on the frog's heart.

The reason for the increased rate and force of the heart beat during the first few minutes of the application of 1 and 2 per cent. alcohol was evidently paralysis of the inhibitory nervous mechanism of the heart, as shown by electrical stimulation of the pneumogastric nerve. The inhibitory nerves were depressed or paralyzed before the heart muscle began to yield to the toxic action of the alcohol. The result was that the heart, relieved of the controlling and regulating influence of the inhibitory nerves, beat faster and more strongly until depressed by the alcohol. It will be observed that in these experiments no attention is given to the action, real or fancied, of alcohol upon digestion, blood-pressure, nerve cells in the cerebral cortex, etc. The only thought in mind in undertaking the experiments was to determine whether alcohol, coming in direct contact with the heart muscle, would act as a stimulant to the action of that muscle or not. The author feels justified in concluding that alcohol is not a stimulant to heart muscle, but rather a depressant and a poison.

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BLOOD PRESSURE IN HAEMORRHAGE AND ITS RESTORATION

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Haemorrhage lowers blood pressure, but the fall in pressure is not invariably proportionate to the amount of blood lost. As is stated by Pilcher and Sollmann, the relation of the fall of blood pressure to the amount of blood lost varies in each animal, but the median type is approached more or less closely in each case. As is further stated by the same authors, the low blood pressure level, or the blood pressure in shock, depends chiefly on the amount of blood lost and not to an important degree on the rapidity of the haemorrhage (1).

In performing the experiments that will be referred to in this paper we were actuated by a desire to learn just what results could be hoped for in endeavoring to restore the blood pressure to normal after haemorrhage. For experimental purposes rabbits were used. They were anaesthetized by the administration through the stomach tube of 1.5 cc. of paraldehyde per kilogram of body weight. The haemorrhage was accomplished by withdrawing from the femoral artery blood in the proportion of 5 cc. per kilogram of body weight, and continuing to withdraw equal amounts until the blood pressure was reduced to the desired level. Intravenous injections of normal saline solution were then made in amounts sometimes less than, in others equal to, and in still others greater than, the amount of blood lost.

In general it may be stated that removal from the circulation of 5 cc. of blood per kilogram is without influence on the blood pressure. Upon the withdrawal of the second portion of 5 cc. per kilogram blood pressure begins to fall and there is a fairly constant fall of pressure with the removal of each successive portion until 20 cc. or 25 cc. per kilogram have been withdrawn. The fall of blood pressure with the loss of each 5 cc. of blood per kilogram averages 6 mm. of mercury (Group 1). After 20 cc. or 25 cc. per kilogram have been removed the loss of more blood causes a more rapid fall in pressure. At this

point we found that each 5 cc. of blood lost per kilogram caused an average fall in blood pressure of 10 mm. (Group 2), and when 35 cc. to 40 cc. per kilogram had been lost the animal was in a condition of shock with a blood pressure varying in different animals from 22 mm. to 35 mm. of mercury.

If normal saline solution be injected during the first stage of haemorrhage, that is while the blood pressure is falling slowly, there is a rapid and permanent return to normal. This may be seen by reference to the tabulated report of group 1.

Group I

EXPERIMENT	HAEMORRHAGE IN CUBIC CENTIMETERS PER KILOGRAM	5	10	15	20	25	NORMAL SALINE IN CUBIC CENTIMETERS PER KILOGRAM	BLOOD PRESSURE AFTER INJECTION
A1	Blood pressure, 80	80	77	72	66	60	30	75
A2	Blood pressure, 84	82	76	69	61	53	25	73
A3	Blood pressure, 81	80	73	64	55		15	76
A4	Blood pressure, 84	80	71	66	59		20	82
A5	Blood pressure, 82	81	75	69			10	79

The first blood pressure recorded is that at the beginning of the experiment, before any blood had been withdrawn. The figures given for blood pressure represent millimetres of mercury.

If the injection of normal saline solution be made during the second stage of haemorrhage, that is during the period of rapid fall in blood pressure, the permanent return of pressure to normal can be accomplished, but the response is much slower than in the first stage. Immediately following the saline infusion the pressure rises 20 mm. or even 30 mm. In one case it rose 38 mm. After the initial rise the return to normal is slow and requires from twenty-four hours to forty-eight hours.

Group II

EXPERIMENT	HAEMORRHAGE IN CUBIC CENTIMETERS PER KILOGRAM	5	10	15	20	25	30	35	SALINE IN CUBIC CENTIMETERS PER KILOGRAM	BLOOD PRESSURE
B1	Blood pressure, 81	80	73	65	58	50	39	28	45	58
B2	Blood pressure, 85	82	74	66	58	53	40	30	35	55
B3	Blood pressure, 80	80	73	67	60	52	46	35	30	73
B4	Blood pressure, 86	84	80	71	63	51	41		30	61
B5	Blood pressure, 82	79	68	59	47	39	30		40	48

If the injection of saline solution be deferred until the third stage of haemorrhage, i.e., until collapse has occurred, the possibility of bringing about a permanent restoration of blood pressure is remote. The first effect of the saline injection is a rise of pressure, this rise usually being about 10 mm., though in one case that will be referred to again it was 20 mm. Repeated injections of large amounts of saline solution were without further effect under these conditions except in the case mentioned. In this case the method followed was the same as in four others. Blood pressure was reduced to 45 mm. of mercury by successive bleedings, the total amount of blood lost being 40 cc. per kilogram. Prompt administration was made of 50 cc. of saline solution per kilogram with rise in blood pressure of 20 mm. As the blood pressure began to decline a further injection of 50 cc. of saline solution per kilogram was given. A third injection of 30 cc. per kilogram was made with the result that there was a gradual return to normal. The course of this experiment is shown in group 3, experiment C4. The four other animals that suffered loss of the same amount of blood, except C2 which was bled to the extent of 35 cc. per kilogram, were treated in the same way and showed an initial rise of pressure of 10 mm. as an average. This soon began to decline and repeated injections of saline solution were without effect.

Group III

EXPERIMENT	HAEMORRHAGE IN CUBIC CENTIMETERS PER KILOGRAM	5	10	15	20	25	30	35	40	SALINE IN CUBIC CENTIMETERS PER KILOGRAM	BLOOD PRESSURE
C1	Blood pressure, 125	120	111	102	92	76	60	44	26	50	35
C2	Blood pressure, 128	124	113	100	85	74	55	35		50	41
C3	Blood pressure, 127	126	119	109	100	90	77	57	23	50	0
C4	Blood pressure, 120	119	111	99	90	80	71	59	45	50	65
C5	Blood pressure, 135	132	120	107	95	83	67	53	37	50	50

In group 3 cats were used instead of rabbits. They were anaesthetized by the administration of ether by inhalation. The initial blood pressure was higher than in the rabbits, but the results are comparable with those obtained in the first two groups of experiments. At first rabbits were tried but they succumbed very quickly after the removal of 35 cc. or 40 cc. of blood per kilogram. Then cats were resorted to with slightly better results as has been recorded.

Pilcher and Sollmann explain the rise in blood pressure as due to stimulation of the vaso-motor centre causing vaso-constriction. They state that the vaso-motor centre is not affected by infusion of saline solution if the blood pressure be 60 mm. of mercury or above, but that when the blood pressure is below 60 mm. the vaso-motor centre may be stimulated by such injections (2). The author's results corroborate this assertion, at least so far as the influence of saline infusions when the blood pressure is below 60 mm. is concerned. No attempt was made to determine the effect of intravenous administration of saline solution at higher blood pressure levels as the experiments were undertaken for a different purpose. The object, as already stated, was to determine what could be hoped for in the way of restoring blood pressure and maintaining the circulation in cases of haemorrhage of varying degrees of severity. From these observations we draw the conclusion that so long as the haemorrhage has not been great enough to reduce blood pressure to the "shock level" gratifying results may be hoped for from the intravenous administration of normal salt solution. When the blood pressure has reached the level of shock, 30 mm. to 50 mm., restoration of blood pressure and maintenance of the vital functions of the organism are a possibility, but cannot be expected with any certainty. In general it can be stated that in haemorrhage injection of amounts of saline solution in excess of the amount of blood lost will give the best results; in severe cases the use of large amounts of normal salt solution, 50 cc. to 100 cc. per kilogram of body weight, is most likely to be attended by a successful outcome.

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SECRETIN

IV. The Number of Red and White Corpuscles in the Circulating Blood During Digestion

BY

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SECRETIN

IV. THE NUMBER OF RED AND WHITE CORPUSCLES IN THE CIRCULATING BLOOD DURING DIGESTION

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In a previous report (1) we have shown that in the rabbit the subcutaneous injection of secretin brings about a considerable increase in the number of red and white corpuscles in the blood stream by directly stimulating the production of new cells. Bayliss and Starling (2) in their original investigation of the pancreatic mechanism demonstrated the presence of secretin in the intestine of the rabbit as well as in that of man, the cat, dog and other animals, and concluded that it is an identical substance in all the vertebrata. According to the hypothesis of these authors and the actual demonstration of Wertheimer (3) secretin is carried in the blood during digestion and should then be at least as potent a stimulus to blood cell formation as when experimentally introduced into the circulation. The examination of the peripheral blood during digestion, therefore, ought to reveal a change in the corpuscle content comparable with our experimental findings, i.e., an increase in the number of erythrocytes and leucocytes per unit volume.

The first work in this connection appears to have been done by Moleschott (4) in 1854. He found an increase in the proportion of white corpuscles to erythrocytes which was particularly marked if the diet was rich in protein food. Hofmeister (5) in 1887 called attention to the "cellular richness" of the adenoid tissue of the intestinal wall during digestion on a meat diet and Pohl (6) went on to show that an increase in the number of white corpuscles in the circulating blood appears early in digestion and persists for several hours. Goodall, Gulland and Paton (7) and Gulland and Paton (8) went into this subject in greatest detail and found in dogs that the maximum leucocyte count occurs three to four hours after a meal. They also showed

this to be chiefly due to a very constant increase in the number of lymphocytes, contributed to much less regularly by a relative increase in the polymorphonuclear cells. They further demonstrated that the source of the leucocytosis is entirely, or almost entirely, the bone marrow in which they found an increased rate of production of white corpuscles during digestion.

Much fewer are the reported observations upon the erythrocytes during digestion. Pohl (6) found a slight diminution in their number, but he made very few determinations and did not follow the count through the entire period of digestion in any case. Buntzen and Sörensen (9) reported an increase of 8 to 25 per cent and Andressen (10) a decrease of 5 to 12 per cent in the number of erythrocytes per unit volume of blood in digestion. In estimations made before and after feeding Goodall, Gulland and Paton (7) found no change in the percentage of haemoglobin.

Källmark (11) in fasting experiments on rabbits found a slight falling off in the total leucocyte count during the fast and, as the most marked change in the differential count, a relative diminution of the lymphocytes. When the animals were again fed the total leucocyte count and the relative proportion of lymphocytes both increased above the original level. If the rabbits were allowed plenty of water he noted no change in the number of erythrocytes. According to Cabot (12) "food calls forth a greater leucocytosis in proportion as it is a novelty to the stomach." Rogers (13) and Swirski (14) in their work on the hunger contractions of the rabbit's stomach found that, even if the rabbits were put in a wire-bottomed cage, when all food was withheld they would eat their excreta and their stomachs would remain continuously partly filled; but if the animal's head was suitably fastened, the stomach completely emptied itself in about twenty-four hours. Therefore, the slight changes observed by Källmark may possibly be explained by his apparent failure to insure a total fast in his rabbits in some such manner.

We have been unable to find any record of blood counts during digestion in rabbits which have been made to endure a total fast. In view of this fact it seemed worth while to undertake such an investigation of the red and white corpuscles.

For this purpose apparently normal rabbits were selected and placed in a contrivance which might be aptly described as a pillory. This consisted of a box partitioned into two compartments. The partition was in two halves, an upper and a lower, in each of which was a rounded

opening. These together made an ovoid aperture through which passed the neck of the rabbit. When in use the rabbit's head projected on one side of the partition while his body was on the other side. With the animal thus fixed an absolute fast was readily maintained. Each rabbit was kept in this box forty to forty-four hours without food but was given as much water as it would drink.

At the end of the fasting period both the red and white corpuscles were counted. The animal was then released and put into a cage where it had free access to food and water. The food in every case consisted of green cabbage and oats. The rabbit always began eating at once and ate more or less continuously all day. Erythrocyte and leucocyte counts were made hourly for the six hours following the beginning of the feeding. As in our previous work the blood was obtained from the ear of the rabbit. The diluting fluids used were 0.5 per cent acetic acid for the white corpuscles and physiological saline solution for the red corpuscles. The counts were made in the usual manner with the Thoma-Zeiss apparatus.

We have made in all ten determinations, the results of which are summarized in tables 1 and 2. These show an average increase of 76.78 per cent in the white corpuscles and of 18.65 per cent in the red corpuscles. The maximum leucocyte count occurred 3.2 hours, and the maximum erythrocyte count 1.9 hours after the feeding started.

To what extent are these changes in the corpuscle content of the blood during digestion in the rabbit comparable with the effect of the experimental administration of secretin? The subcutaneous injection of 1 cc. of secretin solution (10 mgm. of a dried acid extract) per kilogram of body weight is capable of causing in the rabbit an increase in the red corpuscles per unit volume of blood of 17.07 per cent, appearing in 50 minutes and persisting 63.33 minutes. The same dose will bring about an increase in the white corpuscles per unit volume of 44.2 per cent, appearing in 51 minutes and persisting 78.5 minutes (15). This experimental effect of secretin is less, appears more quickly and persists for a shorter time than the findings in digestion noted above. Assuming that secretin is responsible for the latter one would expect such differences. Our experimental solution must necessarily be less active than the secretin entering the blood during digestion; a certain delay must ensue after the feeding starts before food begins to leave the stomach and secretin to be formed; also the formation of secretin and its entrance into the circulation is presumably continuous though not uniform throughout digestion once the process is started.

As mentioned above Gulland and Paton (8) determined that the source of the digestion leucocytosis is an increased rate of production of white corpuscles by the bone marrow. We have demonstrated

TABLE 1

Red corpuscles during digestion in the rabbit

ANIMAL	COUNT BEFORE FEEDING	1ST HOUR	2D HOUR	3D HOUR	4TH HOUR	5TH HOUR	6TH HOUR	PERCENTAGE INCREASE	MAXIMUM IN
									hrs.
1	5,920,000	5,788,000	6,504,000	5,456,000	5,920,000	5,888,000	5,408,000	9.86	2
2	6,584,000	7,360,000	7,712,000	6,920,000	6,320,000	6,064,000	6,368,000	17.13	2
3	5,968,000	5,624,000	5,464,000	6,800,000	7,136,000	4,960,000	5,352,000	19.56	4
4	5,756,000	7,040,000	6,144,000	6,544,000	6,208,000	6,960,000	6,378,000	22.30	1
5	5,488,000	6,320,000	6,880,000	5,896,000	6,008,000	5,600,000	6,192,000	25.36	2
1	5,536,000	6,736,000	5,784,000	4,976,000	6,176,000	5,886,000	5,320,000	21.67	1
2	6,032,000	7,328,000	6,288,000	5,792,000	6,304,000	5,360,000	5,304,000	21.48	1
6	5,736,000	6,128,000	6,512,000	4,800,000	5,600,000	6,092,000	5,720,000	13.52	2
7	6,240,000	6,560,000	6,880,000	6,592,000	5,936,000	5,864,000	5,896,000	10.25	2
8	6,200,000	6,960,000	7,776,000	7,008,000	5,876,000	5,916,000	6,164,000	25.41	2

TABLE 2

White corpuscles during digestion in the rabbit

ANIMAL	COUNT BEFORE FEEDING	1ST HOUR	2D HOUR	3D HOUR	4TH HOUR	5TH HOUR	6TH HOUR	PERCENTAGE INCREASE	MAXIMUM IN
									hours
1	8,000	22,000	16,600	16,000	20,000	16,000	12,000	175.00	1
2	10,000	15,000	13,000	12,700	16,000	10,000	6,600	60.00	4
3	14,000	15,000	24,000	18,600	13,000	21,800	15,000	71.42	2
4	15,000	18,000	19,000	22,400	20,000	20,700	12,600	49.33	3
5	23,400	24,000	28,000	18,000	25,000	20,000	17,600	19.65	2
1	11,000	12,000	15,000	16,000	14,200	19,400	14,000	76.36	5
2	9,600	11,500	13,000	17,500	16,800	17,000	9,000	82.29	3
6	16,000	14,000	22,100	19,000	35,000	18,400	14,000	118.74	4
7	13,200	12,500	21,600	18,000	22,000	14,000	12,000	66.66	4
8	12,400	13,200	16,000	17,000	18,400	16,400	14,500	48.38	4

(1) that secretin acts by directly stimulating the production of both red and white corpuscles by the bone marrow. May it not be that the increased activity of the bone marrow in digestion is the result of the direct stimulating action of secretin?

Additional evidence of the change in the corpuscle content of the blood during digestion being due to secretin is afforded by the differential leucocyte count. The findings of Goodall, Gulland and Paton (7) and of Källmark (11) indicate that, while the change in the leucocyte count during digestion is participated in by all the varieties of white cells, the greatest increase occurs in the lymphocytes. We have previously reported (16) the differential leucocyte count after the administration of secretin as compared to the normal; there also, while all forms are increased in number, the lymphocytes show the greatest relative increase.

CONCLUSIONS

1. During digestion there occurs an increase in the number of both the red and white corpuscles per unit volume of blood.
2. These changes are comparable with the effects produced by the experimental administration of secretin.
3. The source of the increased corpuscle content of the blood both in digestion and after the administration of secretin is an increased rate of production of new cells by the bone marrow.
4. The similarity between the differential leucocyte counts in digestion and after the administration of secretin is additional evidence of secretin being the cause of the increase in the number of corpuscles during digestion.

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III. ITS MODE OF ACTION IN PRODUCING AN INCREASE IN THE NUMBER OF CORPUSCLES IN THE CIRCULATING BLOOD

BY

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In previous reports (1), (2) we have pointed out that secretin is capable of producing a considerable increase in the number of erythrocytes and leucocytes in the circulating blood. We have further suggested that the increase is due to an increased production of blood corpuscles probably by direct stimulation of both the bone marrow and the lymph glands. If this be true its repeated administration over a long period of time should effect definite changes in the blood picture and, in the organs, the histological changes of increased activity.

In accordance with this idea secretin was given hypodermatically to two rabbits to a total of forty doses. The preparation of secretin employed was a dried acid extract as in our previous experiments (2), and the dose of 10 mgm. per kilogram of body weight was dissolved in 2 cc. of physiological saline solution. To each of two control rabbits 2 cc. of physiological saline solution were administered subcutaneously at the same time and under the same conditions. The injections were made every day for two weeks, three times a week for the next two weeks, then every day for the third two weeks, and finally three times a week for two weeks. Thus the entire time during which the experiments were conducted was eight weeks, from December 10, 1917 to February 4, 1918. Each pair of rabbits comprised a male and a female and for convenience will be referred to hereafter as the secretin rabbits, nos. 1 and 2, and the control rabbits, nos. 3 and 4. They were fed and cared for under our personal supervision. We wish to emphasize particularly that there was at no time evidence of infection in any of the rabbits, nor did either of the females become pregnant. Their appearance remained perfectly normal and all showed satisfactory gain in weight, the average for the four animals being 257 grams during the time under observation.

Daily at first but somewhat less frequently later in the course of the experiments, prior to giving the injections, blood was withdrawn from the ear of each rabbit for counting both the red and white corpuscles. The counts were made early in the morning before the animals were fed. Physiological saline solution and 0.5 per cent acetic acid were used as diluting fluids for the red and white corpuscles respectively and the counts were made in the usual manner with the Thoma-Zeiss apparatus. Blood smears were obtained at the same time, subsequently stained and differential leucocyte counts made, the results of which will be detailed later.

Table 1 gives the initial erythrocyte and leucocyte counts in each of the secretin rabbits made before the first injection and the counts week by week, these latter being in each instance the average of all the counts made on that particular animal during the week. Table 2 gives the corresponding counts for the control rabbits. At the bottom of each table is also given the percentage relation of the various counts, considering the initial count as 100 in each case.

A considerable increase in the leucocyte count was promptly produced in the secretin rabbits. This amounted to 52.52 per cent in the first week; in the third week the increase was 146.69 per cent, and even in the eighth week the total leucocyte count was still 37.56 per cent above the initial count in these rabbits. The control rabbits, meanwhile, showed comparatively slight daily variations in the leucocyte count. On two occasions the weekly average was as much as 20 per cent above the initial count but these high counts were evidently only manifestations of the variation that normally occurs in the number of white corpuscles in the rabbit. The leucocytes in the control rabbits did not show the same great and persistent increase in number that was apparent in the secretin rabbits.

Less pronounced change in the erythrocyte count was effected though a comparison of the two tables permits the observation that, while the initial count in the control rabbits was higher than in the secretin rabbits, at the end of the experiment the count in the secretin rabbits was not only relatively greater, 18.47 per cent, but also absolutely higher. We have observed before that the erythrocyte count in normal rabbits may increase to some extent during long periods under observation probably because the living conditions, food, etc., are improved. The increase in the count in the secretin rabbits, however, is greater and occurred more promptly than any effect we have ever observed in normal animals as the result of environmental improvement alone.

TABLE 1

Erythrocyte and leucocyte counts in secretin rabbits

NUMBER		INITIAL COUNT	FIRST WEEK AVERAGE	SECOND WEEK AVERAGE	THIRD WEEK AVERAGE	FOURTH WEEK AVERAGE	FIFTH WEEK AVERAGE	SIXTH WEEK AVERAGE	SEVENTH WEEK AVERAGE	EIGHTH WEEK AVERAGE
1	W. B. C.	9,300	17,183	22,166	22,266	25,833	29,300	16,250	17,400	13,100
	R. B. C.	6,608,000	5,929,000	4,703,000	6,150,000	5,178,000	6,858,000	6,300,000	6,944,000	7,562,000
2	W. B. C.	10,400	12,866	12,916	26,133	20,333	13,000	14,200	16,950	14,000
	R. B. C.	4,432,000	4,941,000	5,208,000	6,150,000	5,042,000	6,715,000	6,336,000	7,196,000	7,332,000
Averages....	W. B. C.	9,850	15,024	17,541	24,199	22,933	21,150	15,125	17,150	13,550
	R. B. C.	5,520,000	5,435,000	4,955,500	6,150,000	5,110,000	6,786,500	6,318,000	7,070,000	7,447,000
Percentage relations	W. B. C.	100.00	152.52	178.08	246.69	232.82	214.63	153.55	174.03	137.56
	R. B. C.	100.00	98.46	89.77	111.41	92.57	122.94	114.45	128.07	134.90

TABLE 2

Erythrocyte and leucocyte counts in control rabbits

NUMBER		INITIAL COUNT	FIRST WEEK AVERAGE	SECOND WEEK AVERAGE	THIRD WEEK AVERAGE	FOURTH WEEK AVERAGE	FIFTH WEEK AVERAGE	SIXTH WEEK AVERAGE	SEVENTH WEEK AVERAGE	EIGHTH WEEK AVERAGE
3	W. B. C.	7,100	7,833	7,166	11,800	7,833	7,600	6,800	9,000	8,533
	R. B. C.	6,272,000	5,536,000	5,784,000	6,121,000	5,386,000	6,336,000	6,574,000	6,616,000	7,250,000
4	W. B. C.	9,800	9,166	6,916	9,100	9,600	10,100	11,250	12,600	10,433
	R. B. C.	6,176,000	6,081,000	6,194,000	6,253,000	6,377,000	7,530,000	6,856,000	6,481,000	7,244,000
Averages....	W. B. C.	8,450	8,499	7,041	10,450	8,716	8,850	9,025	10,800	9,483
	R. B. C.	6,224,000	5,808,500	5,989,000	6,187,000	5,886,500	6,933,000	6,715,000	6,548,500	7,247,000
Percentage relations	W. B. C.	100.00	100.57	83.31	123.66	103.14	104.73	106.80	127.69	112.22
	R. B. C.	100.00	93.35	96.25	99.44	94.60	111.39	107.89	105.21	116.43

Because the blood picture did not show progressive change during the last two weeks of the experiment, we concluded that maximum effect had been obtained. Accordingly the animals were killed and autopsies performed at this time, the method of procedure, practically that described by Livingston (3), being briefly as follows: Each was killed by illuminating gas and weighed before and after expressing the urine. They were then freely bled by being suspended head downward and the abdomen compressed after cutting both carotid arteries and jugular veins. The alimentary tract from the cardia to the anus was excised, weighed and reweighed after its contents had been expressed. We now had the reduced body weight, i.e., the weight of the animal minus the urine and contents of the gastro-intestinal canal.

In general the gross appearance of the tissues was normal in all four animals. Careful inspection showed absolutely no evidence of any infection having existed. The thyroids, spleen and liver were removed from each rabbit and weighed. These weights expressed in milligrams or grams per kilogram of reduced body weight, together with the data from which the reduced body weight was computed, are given in table 3.

TABLE 3

ANIMAL	NUMBER	WEIGHT WHEN KILLED	WEIGHT MINUS URINE	WEIGHT OF GASTRO-INTESTINAL TRACT AND CONTENTS	WEIGHT OF GASTRO-INTESTINAL TRACT MINUS CONTENTS	REDUCED BODY WEIGHT K. B. W.	WEIGHT OF THYROIDS IN MILLIGRAMS PER KILO OF R. B. W.	WEIGHT OF SPLEEN IN MILLIGRAMS PER KILO OF R. B. W.	WEIGHT OF LIVER IN GRAMS PER KILO OF R. B. W.
Secretin.....	1	1890.0	1883.0	356	207.0	1734.0	138.4	991.9	44.994
	2	2249.0	2242.0	322	179.0	2099.0	94.8	819.4	40.752
	Averages	2069.5	2062.5	339	193.0	1916.5	116.6	905.65	42.873
Control	3	2649.0	2649.0	451	304.0	2502.0	86.3	479.6	46.163
	4	1867.0	1844.0	299	179.0	1724.0	64.3	330.6	32.215
	Averages	2258.0	2246.5	375	241.5	2113.0	75.3	405.1	39.189

The thyroids in the secretin rabbits were 54.84 per cent heavier than in the controls, a greater difference than one would expect from individual variations as reported by Livingston (4). Also rabbits 1 and 2 showed slight enlargement of the liver, 9.37 per cent, as compared with the others; and the spleen was more than twice as large as in rabbits 3 and 4, 123.56 per cent.

There was no obvious enlargement of the lymph glands in the secretin rabbits though the cervical and abdominal chains were readily found. Rabbit 3, one of the controls, showed excessive subcutaneous fat, rendering the isolation of lymph nodes in this animal unsatisfactory. Lymph glands from each of the other three were preserved for histological examination.

Finally the head of the tibia in each animal was split open and the cylinder of red marrow carefully removed. In the controls this was of a light pink color, quite soft and very friable. In the others it was considerably darker in color, much more firm and decidedly less friable. These cylinders of marrow were also preserved for histological study. In addition smears of the marrow were made, several from each specimen and as uniform in thickness as possible. These were stained with Wright's stain by the same method employed for blood smears. The difference in the consistency of the marrow from the two pairs of rabbits was very noticeable in the making of the smears. When they were examined microscopically striking differences were observed strongly suggestive of increased activity on the part of the bone marrow of the secretin rabbits.

On the slides from the controls the cells were not numerous being mostly myelocytes with occasional large mononuclear lymphocytes and polymorphonuclear leucocytes. Nucleated red corpuscles were comparatively infrequent. In many fields they were not present and very rarely was more than one seen in a single field. The nuclei of these erythroblasts were deeply stained and quite uniform in appearance. On the other hand, in the smears from the secretin rabbits cells of all types were much more numerous, the most pronounced difference being seen in the nucleated red cells. One or more of these was found in every field and not infrequently as many as six or eight and often more were present in a single field. Furthermore, in most of these the nuclear network was plainly distinguishable and many of these cells were observed which were apparently undergoing cell division presenting various stages of mitosis. Several erythroblasts were also encountered in which the nucleus appeared to be undergoing extrusion. A number of myelocytes were also observed in the process of division. All types of leucocytes were likewise more numerous in these smears.

The absolute increase in the number of cells in one set of slides as contrasted with the other can hardly be attributed solely to unavoidable differences in thickness as the same variation was uniformly shown by all of them. The repeatedly observed evidence of cell division certainly would seem to indicate increased activity.

The cylinders of red marrow and the lymph glands were fixed in Müller's-formalin solution and embedded in celloidin. Sections were cut of a uniform thickness of eight microns and stained with Ehrlich's haematoxylin and alcoholic eosin.

The appearance of the sections of bone marrow from the controls corresponded closely with the usual depiction of normal red marrow, consisting of a rather loose network of cells with large spaces probably previously filled with fat. In the other sections the supporting reticulum could with some difficulty be made out but the spaces were closely packed with cells. These were chiefly myelocytes and erythroblasts with the former predominating. Only rarely small vacuo es were seen, fat cells probably. The myelocytes and erythroblasts, as in the smears, presented evidence of cell division. The absolute number of non-nucleated red corpuscles was greater in the secretin sections than in the controls. There can therefore be no doubt that the bone marrow was much more active in the rabbits which had been given secretin than in those to whom saline had been administered.

In the case of the lymph glands the evidence of increased activity was less striking. While the glands grossly were not obviously enlarged they were very readily found in the secretin rabbits even though no. 2 was quite as fat as no. 3 of the controls in which we were unable to isolate any glands satisfactorily for sectioning. The lymph gland sections showed the cells more closely packed in the glands from the secretin rabbits than in those from the controls. In the former the cells almost overlapped in some cases, whereas in the latter they were surrounded by free spaces at least as wide as the cells and usually wider.

The number of white corpuscles in the circulating blood of the secretin rabbits would seem to be directly proportional to their increased production, but the evidence of increased production of red corpuscles far surpasses the increase in the erythrocyte count. For this reason the question naturally presents itself: If such greatly increased activity of the bone marrow is produced by secretin, why is there not a greater and more persistent increase in the number of erythrocytes in the circulating blood? A clue to the answer to this question would seem to be afforded by the enlargement of the liver and spleen. According to Robertson and Rous (5) overactivity on the part of the bone marrow results in the production of immature erythrocytes whose resistance to disintegration in the blood stream is below normal. The remains of these corpuscles which have gone to pieces throughout the circulation

are removed from the blood chiefly by the spleen but partly also by the liver. The accumulation of this debris, according to the same authors, is the chief cause of the enlarged spleen in anaemias. Possibly we have a similar condition brought about by the repeated administration of secretin, which is obviously producing overstimulation and therefore conceivably causing the production of less perfect corpuscles which undergo disintegration in the blood stream and are removed by the spleen and liver.

Another explanation of the apparent discrepancy between the production of the red corpuscles and the number in circulation is also to be found in the activity of the liver. It has been repeatedly demonstrated that secretin stimulates the secretion of bile (6), (7). Possibly this increased production of bile requires and brings about an increased destruction of the red corpuscles which is only a little more than offset by their increased production. Here again the enlargement of the spleen would have to be explained by accumulation in it of fragmented corpuscles. A direct relation between the disintegration of the red corpuscles with the liberation of haemoglobin and the secretion of bile pigment is claimed by Eppinger and Charnas (8), Wilbur and Addis (9) but denied in the more recent work of Whipple and Hooper (10).

Further evidence of the production of new corpuscles in response to secretin can be adduced from the study of the blood smears. The material for this study was obtained coincidentally with the making of the leucocyte counts in the experiments recorded in a previous paper (2) and, as previously mentioned, from the animals used in the preparation of the present report. The blood smears were stained according to the method recommended by Russell (11), viz., Wright's stain, 2 minutes; water, 5 minutes; dilute Manson's stain, 40 seconds; washed and dried. In every case at least two hundred cells were counted for deriving the percentages and the usual number counted was three hundred. Ehrlich's classification of the white corpuscles has been followed simply because it is so widely known.

We have made altogether sixteen determinations of the differential leucocyte count in apparently normal rabbits as they came to us before they were subjected to any experimental procedure. An average of the sixteen determinations gives us the following figures: Total count, 10,372 white corpuscles per cubic millimeter of blood; small mononuclear lymphocytes, 7.5 per cent; large mononuclear lymphocytes, 13.3 per cent; transitional leucocytes, 5.4 per cent; polymorphonuclear

neutrophilic leucocytes, 69.7 per cent; polymorphonuclear eosinophilic leucocytes, 3.6 per cent; polymorphonuclear basophilic leucocytes, 0.5 per cent (table 4).

Differential leucocyte counts were also made from smears obtained at the time of maximum count in ten experiments in each of which the rabbit had been given subcutaneously a single dose of 1 cc. of secretin solution (10 mgm. of the dried acid extract) per kilogram of body weight. The details of these experiments have been recorded pre-

TABLE 4

Differential leucocyte counts in normal rabbits

NUMBER	TOTAL COUNT	LYMPHOCYTES		LEUCOCYTES			
		Small	Large	Transitional	Neutrophile	Eosinophile	Basophile
1	9,300	14.2	11.0	6.8	63.5	4.0	0.5
2	10,400	10.3	15.0	6.0	66.0	2.0	0.7
3	7,100	6.0	16.0	6.0	68.0	3.0	1.0
4	9,800	9.0	12.0	5.0	69.7	4.0	0.3
5 (1)*	4,800	7.0	13.3	4.5	67.6	7.3	0.3
6 (2)	10,400	7.0	9.0	5.0	74.0	4.7	0.3
7 (3)	9,600	5.0	15.0	6.0	69.0	4.5	0.5
8 (4)	6,200	2.7	10.7	5.6	77.0	3.5	0.5
9 (5)	11,600	10.3	11.3	3.0	72.0	3.0	0.4
10 (6)	20,000	8.0	13.5	4.0	70.0	4.0	0.5
11 (7)	15,600	10.0	13.5	6.0	67.0	3.0	0.5
12 (8)	12,654	4.0	17.0	6.0	70.5	2.0	0.5
13 (9)	10,900	7.0	18.0	6.0	65.5	3.0	0.5
14 (10)	7,400	8.5	10.5	5.5	73.0	2.0	0.5
15 (15)	11,000	5.0	15.0	6.0	70.0	3.5	0.5
16 (16)	9,200	6.0	12.0	5.0	72.4	4.1	0.5
Averages.....	10,372	7.5	13.3	5.4	69.7	3.6	0.5

* In this and succeeding tables the bracketed figures are the experiment numbers of previous report (2).

viously (2). Averaging these ten counts we get the following figures: Total count, 15,113 white corpuscles per cubic millimeter, which was an average increase of 44.2 per cent as compared with the initial counts in the same ten experiments; small mononuclears, 14.01 per cent; large mononuclears, 14.28 per cent; transitionals, 4.3 per cent; polymorphonuclear neutrophiles, 64.55 per cent; polymorphonuclear eosinophiles, 2.42 per cent; polymorphonuclear basophiles, 0.44 per cent (table 5).

TABLE 5

Differential leucocyte counts at time of maximum effect following single dose of secretin

NUMBER	TOTAL COUNT	LYMPHOCYTES		LEUCOCYTES			
		Small	Large	Transitional	Neutrophile	Eosinophile	Basophile
5 (1)	7,800	16.0	6.0	3.0	71.0	3.0	1.0
6 (2)	13,600	17.4	9.0	4.0	67.0	2.3	0.3
7 (3)	11,250	21.0	6.0	3.0	67.0	2.5	0.5
8 (4)	14,200	10.0	11.0	4.5	71.0	3.0	0.5
9 (5)	16,600	21.0	13.0	3.0	60.0	2.7	0.3
10 (6)	34,800	12.0	21.0	5.0	60.0	2.0	0.0
11 (7)	11,786	9.3	19.3	6.0	62.0	2.7	0.3
12 (8)	15,800	8.0	20.0	5.0	64.5	2.0	0.5
13 (9)	13,100	13.0	21.0	5.0	58.5	2.0	0.5
14 (10)	12,200	12.0	16.5	4.5	64.5	2.0	0.5
Averages.....	15,113	14.01	14.28	4.3	64.55	2.42	0.44

Following the administration of secretin, therefore, there is an absolute increase in all varieties of the white corpuscles, a considerable relative increase in the number of the small mononuclear lymphocytes and a slight relative increase in the large mononuclear lymphocytes, with a relative diminution in the polymorphonuclear leucocytes.

Tables 6 and 7 give the total and differential leucocyte counts in two experiments, also previously recorded in full (2), in each of which 1 cc. of secretin solution (10 mgm. of the dried acid extract) per kilogram of body weight was injected subcutaneously at hourly intervals for three doses. Here again there is a relative increase in the mono-

TABLE 6

Experiment 15 (15)

TIME	TOTAL COUNT	LYMPHOCYTES		LEUCOCYTES			
		Small	Large	Transitional	Neutrophile	Eosinophile	Basophile
Initial.....	11,000	5.0	15.0	6.0	70.0	3.5	0.5
1st hour.....	13,300	10.0	17.5	4.0	65.5	2.5	0.5
2d hour.....	11,600	10.5	16.0	5.0	63.5	4.0	1.0
3d hour.....	11,400	15.0	11.0	3.0	66.0	4.0	1.0
5th hour.....	14,600	7.5	10.0	3.0	75.5	3.5	0.5
6th hour.....	11,800	3.0	7.5	3.5	82.0	3.5	0.5

TABLE 7

Experiment 16 (16)

TIME	TOTAL COUNT	LYMPHOCYTES		LEUCOCYTES			
		Small	Large	Transitional	Neutrophile	Eosinophile	Basophile
Initial	9,200	6.0	12.0	5.0	72.5	4.0	0.5
1st hour	15,300	10.0	16.0	5.0	65.0	3.5	0.5
2d hour	13,200	7.7	17.0	5.3	65.7	4.0	0.3
3d hour	12,600	7.0	17.0	4.5	67.5	3.5	0.5
5th hour	16,200	3.5	12.5	3.0	76.5	4.0	0.5
6th hour	12,200	3.0	9.0	4.5	79.0	4.0	0.5

nuclear lymphocytes. Toward the end of the experiment the opposite condition prevails, viz., a relative increase in the polymorphonuclear leucocytes with a relative diminution in the lymphocytes, persisting even after the falling off of the total count. Moreover, we five times observed nucleated red corpuscles in the blood smears of this series, in each instance in a smear obtained after the administration of the third dose of secretin.

We have further recorded the total and differential counts in each of the four rabbits of the present series at irregular intervals throughout the course of the experiment. These figures are given in tables 8, 9, 10 and 11. In this case the secretin rabbits show a slight relative increase in the large mononuclear lymphocytes and also the transitionals with a relative decrease in the small mononuclear lymphocytes and with practically no change in the proportion of the polymorphonuclear leucocytes. For example, averaging the initial counts we get: Total count, 9,850; small mononuclears, 12.25 per cent; large mononuclears, 13.0 per cent; transitionals, 6.5 per cent; polymorphonuclear neutrophiles, 64.75 per cent; polymorphonuclear eosinophiles, 3.0 per cent; polymorphonuclear basophiles, 0.5 per cent; and averaging all the counts made after administration of secretin we get: Total count, 16,300; small mononuclears, 9.37 per cent; large mononuclears, 15.2 per cent; transitionals, 9.56 per cent; polymorphonuclear neutrophiles, 62.12 per cent; polymorphonuclear eosinophiles, 3.0 per cent; polymorphonuclear basophiles, 0.5 per cent. A comparison of the differential counts of the control rabbits fails to show similar variations in the relative proportions of the different types of white corpuscles.

TABLE 8

Differential leucocyte counts in secretin rabbit, no. 1

DATE OF OBSERVATION	TOTAL COUNT	LYMPHOCYTES		LEUCOCYTES			
		Small	Large	Transitional	Neutrophile	Eosinophile	Basophile
December 10, 1917....	9,300	14.0	11.0	7.0	63.5	4.0	0.5
December 19, 1917....	19,600	14.5	9.5	10.5	63.0	2.0	0.5
December 31, 1917....	15,600	10.0	10.0	8.0	68.5	3.0	0.5
January 26, 1918....	18,000	7.0	17.5	10.0	62.0	3.0	0.5
February 2, 1918....	15,400	8.0	17.0	9.0	62.5	3.0	0.5

TABLE 9

Differential leucocyte counts in secretin rabbit, no. 2

DATE OF OBSERVATION	TOTAL COUNT	LYMPHOCYTES		LEUCOCYTES			
		Small	Large	Transitional	Neutrophile	Eosinophile	Basophile
December 10, 1917....	10,400	10.5	15.0	6.0	66.0	2.0	0.5
December 19, 1917....	11,600	9.0	16.0	8.0	63.0	2.5	0.5
December 31, 1917....	20,800	10.0	18.0	10.0	57.0	4.0	0.5
January 26, 1918....	15,200	7.5	17.5	11.0	59.5	4.0	0.5
February 2, 1918....	14,200	9.0	16.0	10.0	61.5	3.0	0.5

TABLE 10

Differential leucocyte counts in control rabbit, no. 3

DATE OF OBSERVATION	TOTAL COUNT	LYMPHOCYTES		LEUCOCYTES			
		Small	Large	Transitional	Neutrophile	Eosinophile	Basophile
December 10, 1917....	7,100	6.0	16.0	6.0	68.0	3.0	1.0
December 19, 1917....	9,200	6.0	17.0	6.0	67.0	3.7	0.3
December 31, 1917....	7,400	5.0	19.0	5.0	66.3	4.0	0.7
January 26, 1918....	10,800	7.0	14.0	5.0	70.5	3.0	0.5
February 2, 1918....	9,200	5.0	16.0	5.0	69.5	4.0	0.5

TABLE 11

Differential leucocyte counts in control rabbit, no. 4

DATE OF OBSERVATION	TOTAL COUNT	LYMPHOCYTES		LEUCOCYTES			
		Small	Large	Transitional	Neutrophile	Eosinophile	Basophile
December 10, 1917....	9,800	9.0	12.0	5.0	69.7	4.0	0.3
December 19, 1917....	6,600	6.0	17.0	6.0	66.5	4.0	0.5
December 31, 1917....	8,200	10.5	15.0	6.0	65.0	3.0	0.5
January 26, 1918....	13,200	8.0	12.0	6.0	69.5	4.0	0.5
February 2, 1918....	10,400	8.0	16.0	5.0	66.5	4.0	0.5

Such alterations in the relative percentages of the different forms of leucocytes, as have been recorded in tables 4 to 11 inclusive, where there is an absolute increase in the total white corpuscle count, is presumptive evidence of the formation of new cells especially of the types relatively increased.

SUMMARY

Therefore, we conclude that the increase in the number of red and white corpuscles per cubic millimeter of circulating blood shown to take place in the rabbit after the administration of secretin is dependent upon increased production of new blood cells. This greater production is apparently due to stimulation of the bone marrow and lymph glands by secretin. The evidence on which this conclusion is based is: the autopsy findings, the changes in the smears of bone marrow, the histological alteration in both the bone marrow and the lymph glands, the variation in the relative proportions of the white corpuscles and the appearance of nucleated red corpuscles in the circulating blood.

We wish to acknowledge the assistance rendered by Messrs. L. and M. Notkin in the conduct of these experiments.

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SECRETIN AND THE CHANGE IN THE CORPUSCLE CONTENT OF THE BLOOD DURING DIGESTION

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SECRETIN AND THE CHANGE IN THE CORPUSCLE CONTENT OF THE BLOOD DURING DIGESTION.

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In 1895 Dolinski (1) showed that acids brought into contact with the mucous membrane of the duodenum set up a secretion of pancreatic juice. Pawlow and his co-workers (2) further decided that the acid acts reflexly through a nerve center. Later Popielski (3), working under the direction of Pawlow, showed that if acids are introduced into the duodenum the pancreatic secretion appears after resection of both vagus and splanchnic nerves, after extirpation of the solar plexus and even after destruction of the spinal cord. He concluded that the secretion arose from a peripheral reflex through scattered ganglia of the pancreas, situated mostly near the duodenum. The same results and conclusions were reached by Wertheimer and Lepage (4). At this point Bayliss and Starling (5) demonstrated the true explanation of the phenomenon. They showed that the acid acts on a substance in the duodenal mucous membrane, prosecretin, and changes it into another substance, secretin. This is carried by the blood and activates the pancreatic cells.

Bayliss and Starling (5) also showed that secretin increase the secretion of bile. We have confirmed this by noting the rate of flow of bile incidentally in the course of other experiments. Sir Edward A. Schaefer (6) states that secretin increases the flow of bile and of succus entericus, but to a less extent than it affects the flow of pancreatic juice. He also states that intravenous injection of duodenal extract (evidently secretin from the context) has been shown by Cow (7) to cause the appearance of the pituitary autacoids in the cerebro-spinal fluid.

Beveridge and Williams (8) in their very ingenious exposition of what they call the proteomorphic theory of immunity claim to have the records of over two hundred cases of diabetes and exophthalmic goiter in which the number of red corpuscles per cubic millimeter of blood was increased by the administration of secretin. Their theory of the production of immunity depends greatly on the power to hydrolyze proteins which they attribute to the red blood corpuscles. If we grant that these premises are correct, then any agent capable of bringing about a sufficient increase in the number of red corpuscles becomes of therapeutic value. If secretin is to exert any influence as an immunizing agent by increasing the number of red corpuscles in the circulating blood, it is obvious that a single dose must be capable of causing a great and fairly prolonged rise in the red corpuscle count. As a means of ordinary treatment, hypodermic medication is preferable to intravenous, and if it can be shown that secretin administered hypodermically is able to increase the number of red corpuscles, then, again, in order to be of service, a single dose, or at most three or four successive doses, should produce and maintain a largely increased erythrocyte count.

Acting in accordance with the ideas thus suggested we determined to try first, the effect of a certain arbitrarily fixed dose of secretin given intravenously, and second, the effect of the same dose when introduced hypodermatically.

In our selection of the animal to be used we were guided by the recent work of Lamson (9) on acute polycythemia in which he has shown that adrenalin, fright, pain, etc., cause sudden and very marked elevation of the red corpuscle count in the dog and cat, but that these agents are without effect on the erythrocyte count of the rabbit. Therefore that we might avoid the use of an anaesthetic, especially in those experiments which were to be continued over several days, in order that the attending conditions might be as uniform as possible, rabbits were employed in all of the experiments herein recorded.

The secretin was in all cases prepared from the intestine of the dog. The animal was anaesthetized by ether alone and the upper half of the small intestine removed. This intestine was carefully washed in running water and the mucous membrane scraped off with a dull knife. The scrapings were rubbed up in a mortar with sand, covered with 50 cc. of 0.4 per cent hydrochloric acid and allowed to stand for an hour or more. The mixture was then boiled actively for several minutes, neutralized with strong potassium hydroxide while boiling and again rendered faintly acid with glacial acetic acid. Finally the preparation was strained through muslin and filtered.

We found that this preparation when kept in the dark retained its potency for about five days; but if glacial acetic acid were added to the filtrate in sufficient quantity to make this 2 per cent acid by volume and the solution evaporated to dryness, the residue was found to retain its potency for at least six months. When required, a weighed quantity could be dissolved in distilled water and neutralized, thus giving a preparation of the same effectiveness as the original solution.

Over two hundred determinations of the red corpuscles per cubic millimeter of blood were made in the course of these experiments, the blood being obtained from the ear of the rabbit and the count made in the usual manner with the Thoma-Zeiss apparatus.

The dose of secretin solution selected for the first experiments was 1 cc. per kilogram of body weight. Five rabbits were taken, the erythrocytes per cubic millimeter of blood counted, and the proper dose of secretin injected into the femoral vein. The average results of this series of experiments follow: Red blood corpuscles per cubic millimeter before the injection of secretin, 4,954,000; maximum count, 6,938,000; amount of increase, 1,984,000; percentage increase, 40.04; maximum attained in 31 minutes; duration of effect 66 minutes.

The next thing to be determined was the effect of this same dose when it was introduced beneath the skin. Accordingly a second series of five experiments was carried out in which the proper dose of secretin was administered subcutaneously. This series gave results as follows: Initial count of red corpuscles per cubic millimeter of blood, 4,990,000; maximum count, 6,102,000; amount of increase, 1,112,000; percentage increase, 22.2; maximum attained in 47 minutes; duration of effect 79 minutes.

The second group of experiments convinced us that secretin injected subcutaneously was capable of exerting an influence, at least so far as affecting the number of red corpuscles in circulation was concerned. Moreover, the greater effect obtained by giving the secretin intravenously was not sufficiently pronounced to make it the method of choice so far as any therapeutic application was concerned. Therefore, we decided to adhere to the method of hypodermic administration in the remainder of our experiments, particularly as these two series of observations appeared to furnish sufficient data from which to deduce the probable action of any particular dose of secretin when given intravenously if we had determined its effect when given hypodermatically.

To determine the most effective dose we made several series of experiments, using the following doses per kilogram of body weight: 0.75 cc., 0.5 cc., 0.25 cc., 1.5 cc., 2 cc. In this way we tested the effect of amounts of secretin less than and greater than the original and arbitrary dose of 1 cc. per kilogram of body weight. Reviewing the average percentage increase with each dose we found the results to be as follows: 0.25 cc. secretin per kilogram of body weight, 11.0 per cent; 0.5 cc. secretin per kilogram of body weight, 10.1 per cent; 0.75 cc. secretin per kilogram of body weight, 17.9 per cent; 1 cc. secretin per kilogram of body weight, 22.2 per cent; 1.5 cc. secretin per kilogram of body weight, 21.2 per cent; 2 cc. secretin per kilogram of body weight, 22.4 per cent. These records indicate a dose of 1 cc. per kilogram of body weight as the most efficient dose of secretin. We also found that the longest average time the effect lasted was ninety minutes—where

the dose was 2 cc. secretin per kilogram of body weight. With a dose of 1 cc. per kilogram of body weight the average duration was 79 minutes.

There was yet to be ascertained the effect, if any, of secretin on the number of white corpuscles per unit volume of blood. Therefore other experiments were performed in which the numbers of both red and white corpuscles were noted. The dose used was 1 cc. per kilogram of body weight and it was given subcutaneously in each case. Table 1 summarizes the results of these experiments.

TABLE 1.

Dose: 1 cc. secretin solution per kilogram of body weight.

Experiment Number.		*Initial count.*	*Maximum count.*	*Amount of increase.*	*Percentage increase.*	*Maximum in minutes.*	*Duration of effect minutes.*
1	W B. C.	4,800	7,800	3,000	62.50	30	65
	R. B. C.	(a)					
2	W. B. C.	10,400	13,600	3,200	30.76	30	60
	R. B. C.	4,960,000	5,608,000	648,000	13.06	30	30
3	W. B. C.	9,600	11,250	1,650	17.18	90	90
	R. B. C.	5,331,000	6,240,000	909,000	17.05	90	90
4	W. B. C.	6,200	14,200	8,000	129.03	30	90
	R. B. C.	7,349,000	7,840,000	491,000	6.68	30	30
5	W. B. C.	11,600	16,600	5,000	43.10	60	90
	R. B. C.	6,054,000	7,184,000	1,130,000	18.66	60	60
6	W. B. C.	20,000	34,800	14,800	74.00	60	90
	R. B. C.	5,234,000	7,200,000	1,966,000	37.56	60	90
7	W. B. C.	15,600	11,786 (b)	3,814	24.44	30	60
	R. B. C.	6,427,000	6,631,000	204,000	3.17	90	90
8	W. B. C.	12,654	15,800	3,146	24.86	60	90
	R. B. C.	6,615,000	7,760,000	1,145,000	17.30	30	60
9	W. B. C.	10,900	13,100	2,200	20.18	60	60
	R. B. C.	5,605,000	6,912,000	1,307,000	23.31	60	60
10	W. B. C.	7,400	12,200	4,800	64.86	60	90
	R. B. C.	5,343,000	6,246,000	903,000	16.90	60	60
Avgs.	W. B. C.	10,915	15,113	4,198	44.20	51	78.5
	R. B. C.	5,879,777	6,846,777	967,000	17.07	60	63.3

(a) Red corpuscle counts were not made in experiment 1.
(b) Experiment 7 shows a decrease in the white corpuscle count.

These results show conclusively that not only is secretin solution, when injected subcutaneously, able to produce an increase in the number of erythrocytes in the circulating blood but that it is capable of producing an even greater effect on the number of white blood corpuscles. In addition, however, it shows that the duration of the effect on the number of the corpuscles and the time of appearance of the maximum count are very nearly the same in the two cases—duration of effect on the red blood corpuscles 63.3 minutes, on the white corpuscles 78.5 minutes; maximum count of red blood corpuscles per cubic millimeter in 60 minutes, of white blood corpuscles per cubic millimeter in 51 minutes—the effect being produced quicker in the case of white corpuscles and persisting longer.

The next question that naturally arises is: How does secretin cause this increase in the number of both red and white corpuscles? The first and simplest explanation that presents itself is that secretin exerts a direct stimulating influence upon the red marrow of the bones and upon the lymph glands, thus leading to the formation of new cells. A second way in which it might bring about an increase in the number of circulating corpuscles is by causing variations in their unequal distribution. This might be effected by a direct constricting action on the vessels of some large area, such as the liver, or by an indirect action through stimulation of the adrenals. From the work of Lamson (9), (10), Cannon (11), and Mautner and Pick (12), it seems that we can rule out the suggestion that secretin increases the number of corpuscles in the circulating blood of the rabbit by stimulating the adrenals. As to whether secretin acts directly to promote

capillary constriction or not we have no evidence and do not know of any work on the subject that has been reported.

If the first explanation offered as to the mode of action of secretin be correct, its repeated administration over a long period of time should effect definite changes in the blood picture and, in the organs, the histological changes of increased activity. Accordingly, secretin was given hypodermatically to two rabbits to a total of forty doses. The preparation of secretin employed was a dried acid extract as in our previous experiments, and the dose of 10 milligrams per kilogram of body weight was dissolved in 2 cc. of physiological saline solution. To each of two control rabbits, 2 cc. of physiological saline solution were administered subcutaneously at the same time and under the same conditions. The injections were made every day for two weeks, three times a week for the next two weeks, then every day for the third two weeks, and finally three times a week for two weeks. Thus the entire time during which the experiments were conducted was eight weeks, from December 10, 1917, to February 4, 1918.

A considerable increase in the leucocyte count was promptly produced in the secretin rabbits. This amounted to 52.52 per cent in the first week; in the third week the increase was 146.69 per cent, and even in the eighth week the total leucocyte count was still 37.56 per cent above the initial count in these rabbits. The control rabbits, meanwhile, showed comparatively slight daily variations in the leucocyte count. On two occasions the weekly average was as much as twenty per cent above the initial count, but these high counts were evidently only manifestations of the variation that normally occurs in the number of white corpuscles in the rabbit. The leucocytes in the control rabbits did not show the same great and persistent increase in number that was apparent in the secretin rabbits. Less pronounced change in the erythrocyte count was effected. However, at the end of the experiment the count was 22.94 per cent higher than at the beginning.

Three days after the last injections were given autopsies were performed upon all the animals and careful macroscopic and microscopic examination made of the various organs. When the bone marrow was examined microscopically, striking differences were noted between the specimens of marrow from the secretin rabbits and those from the controls. These changes were strongly indicative of increased activity in the bone marrow of the rabbits that had received secretin. In the case of these rabbits cells of all types, myelocytes, white corpuscles and erythrocytes, were much more numerous than in the marrow of the controls and there was a very noticeable increase in the number of nucleated red corpuscles present. In the case of the lymph glands the evidence of increased activity was less striking, but sections from the glands of the secretin rabbits showed the cells more numerous and more closely packed than in the glands from the control rabbits.

Bayliss and Starling (13) in their original investigation of the pancreatic mechanism demonstrated the presence of secretin in the intestine of the rabbit as well as in that of man, the cat, dog and other animals, and concluded that it is an identical substance in all the vertebrata. According to the hypothesis of these authors and the actual demonstration of Wertheimer (14) secretin is carried in the blood during digestion and should then be at least as potent a stimulus to blood cell formation as when experimentally introduced into the circulation. The examination of the peripheral blood during digestion, therefore, ought to reveal a change in the corpuscle content comparable with our experimental findings, *i. e.*, an increase in the number of erythrocytes and leucocytes per unit volume.

For this purpose apparently normal rabbits were selected and placed in a contrivance which might be aptly described as a pillory. This consisted of a box partitioned into two compartments. The partition was in two halves, an upper and lower, in each of which was a rounded opening. These together made an ovoid aperture through which

passed the neck of the rabbit. When in use the rabbit's head projected on one side of the partition while his body was on the other side. With the animal thus fixed an absolute fast was readily maintained. Such rigid precautions had to be taken because of the findings of Rogers (15) and Swirski (16). These authors in their work on the hunger contractions of the rabbit's stomach showed that, even if the rabbits were put in a wire-bottomed cage, when all food was withhheld they would eat their excreta and their stomachs would remain continuously partly filled; but, if the animal's head was suitably fastened, the stomach completely emptied itself in about twenty-four hours.

Each rabbit was kept in the box forty to forty-four hours without food, but was given as much water as it would drink. At the end of the fasting period both the red and white corpuscles were counted. The animal was then released and put into a cage where it had free access to food and water. The food in every case consisted of green cabbage and oats. The rabbit always began eating at once and ate more or less continuously all day. Erythrocyte and leucocyte counts were made hourly for the six hours following the beginning of the feeding. We have made in all ten determinations, the results of which are summarized in table 2.

These show an average increase of 16.18 per cent in the white corpuscles and of 18.65 per cent in the red corpuscles. The maximum leucocyte count occurred 3.2 hours, and the maximum erythrocyte count 1.9 hours after the feeding started. The experimental effect of secretin is less, appears more quickly and persists for a shorter time than the findings in digestion noted above. Assuming that secretin is responsible for the latter, one would expect such differences. Our experimental solution must necessarily be less active than the secretin entering the blood during digestion; a certain delay must ensue after the feeding starts before food begins to leave the stomach and secretin to be formed; also the formation of secretin and its entrance into the circulation is presumably continuous though not uniform throughout digestion once the process is started.

These investigations appear to indicate the existence of a mechanism concerned not only in the production of the digestive agents, pancreatic juice and bile, but also in the formation of an increased number of cor-

TABLE 2.

Red and white corpuscles during digestion in the rabbit.

Animal number.	*Count before feeding.*	*First hour.*	*Second hour.*	*Third hour.*	*Fourth hour.*	*Fifth hour.*	*Sixth hour.*	*Percentage increase.*	*Maximum inc.*
1 W. B. C.	8,000	22,000	16,600	16,000	20,000	16,000	12,000	175.00	1 hour
R. B. C.	5,920,000	5,788,000	6,504,000	5,456,000	5,920,000	5,888,000	5,400,000	9.86	2 hours
2 W. B. C.	10,000	15,000	13,000	12,700	16,000	10,000	6,600	60.00	4 hours
R. B. C.	6,584,000	7,360,000	7,712,000	6,920,000	6,320,000	6,064,000	6,368,000	17.13	2 hours
3 W. B. C.	14,000	15,000	24,000	18,600	13,000	21,800	15,000	71.42	2 hours
R. B. C.	5,968,000	5,624,000	5,464,000	6,800,000	7,136,000	4,960,000	5,352,000	19.56	4 hours
4 W. B. C.	15,000	18,000	19,000	22,400	20,000	20,700	12,600	49.33	3 hours
R. B. C.	5,756,000	7,040,000	6,144,000	6,544,000	6,208,000	6,960,000	6,378,000	22.30	1 hour
5 W. B. C.	23,400	24,000	28,000	18,000	25,000	20,000	17,600	19.65	2 hours
R. B. C.	5,488,000	6,320,000	6,880,000	5,896,000	6,008,000	5,600,000	6,192,000	25.36	2 hours
1 W. B. C.	11,000	12,000	15,000	16,000	14,200	19,400	14,000	76.36	5 hours
R. B. C.	5,536,000	6,736,000	5,783,000	4,976,000	6,176,000	5,886,000	5,320,000	21.67	1 hour
2 W. B. C.	9,600	11,500	13,000	17,500	16,800	17,000	9,000	82.29	3 hours
R. B. C.	6,032,000	7,328,000	6,288,000	5,792,000	6,304,000	5,360,000	5,304,000	21.48	1 hour
6 W. B. C.	16,000	14,000	22,100	19,000	35,000	18,400	14,000	118.74	4 hours
R. B. C.	5,736,000	6,128,000	6,512,000	4,800,000	5,600,000	6,092,000	5,720,000	13.52	2 hours
7 W. B. C.	13,200	12,500	21,600	18,000	22,000	14,000	12,000	66.66	4 hours
R. B. C.	6,240,000	6,560,000	6,880,000	6,592,000	5,936,000	5,864,000	5,896,000	10.25	2 hours
8 W. B. C.	12,400	13,200	16,000	17,000	18,400	16,400	14,500	48.38	4 hours
R. B. C.	6,200,000	6,960,000	7,776,000	7,008,000	5,876,000	5,916,000	6,164,000	25.41	2 hours

puscles in the blood at a time when they are needed to care for the absorbed products of digestion.

Conclusions.

1. It is possible to produce a considerable increase in the number of red corpuscles and of white corpuscles in the circulating blood by the administration of secretin even in small doses and by subcutaneous injection.

2. The increase in the count in both cases appear quickly and is very transient.

3. The increase in the number of white corpuscles is greater and more persistent than the increase in the number of erythrocytes.

4. The increase in the number of red and white corpuscles in the circulating blood shown to take place in the rabbit after the administration of secretin is dependent upon increased production of new blood cells due to stimulation of the bone marrow and lymph glands by secretin.

5. During digestion there occurs an increase in the number of both the red and white corpuscles per unit volume of blood.

6. These changes are comparable with the effect produced by the experimental administration of secretin.

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ORIGINAL ARTICLES

HORMONES AND HORMONE THERAPY.*

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Concerning this important subject perhaps none will claim exhaustive knowledge. Judging by the modest words of some of our efficient teachers, scientists who have made organo-therapy an important adjunct to their former armamentarium, we must conclude that in the minds of the foremost there remains much yet to be learned about hormones.

Perhaps one of the best definitions of this word is that given last year before the Royal Society of Medicine by Professor Starling himself, who originated the name hormone soon after he and Bayliss discovered and described secretin in 1902 in the research laboratory of University College, London. His words are as follows:

"By the term hormone I understand any substance normally produced in the cells of some part of the body and carried by the blood stream to distant parts, which it affects for the good of the whole. The hormones are thus chemical means of correlation of the activities of the different parts of the body. Their action may be the increase or diminution of function or the alteration of nutrition or rate of growth."

A list of the organs which secrete these hormones furnishes us some surprises. For many years, to my knowledge, the functions of some of the ductless glands, the spleen, the thymus and thyroid glands and others were entirely unknown or were subjects of debate and wide difference of opinion among physiologists. Larger experience, better means of investigation, and, above all, a more earnest spirit of research by a large number of able men, have contributed to an increase of definite knowledge along these lines. Today a "new physiology" has developed and men abundantly able to teach tell us more or less clearly of the functions of the pituitary gland, the function of one lobe of which differs from that of the others; the functions of the suprarenal capsule, whose cortex is said to produce one effect, while its medulla produces another; of the parathyroids, four little bodies scarcely larger than the head of a pin near the thyroid glands, the physiologic importance of which seems to be altogether out of proportion to their diminutive size, and even of the hormonogenic function of the mammæ, of the testes and of the ovaries, different portions of which produce hormones having different offices to perform. Our teachers tell us, also, that even the liver and the kidneys generate hormones, and the mucous membrane of the duodenum and of the pylorus produces secretin, an important hormone vitally connected with the digestive function of all mammals.

We are taught by the best authorities that both anabolism and catabolism of the entire body, and all the activities of the digestive, circulatory and reproductive systems are more fully under the control of the hormones than they are of the nervous system, the paramount influence of which was so confidently taught only a few years ago.

In the definition of hormones already herein quoted, the author says that development and rate of growth are under the control of the hormones. We ought here to notice a few striking examples of some

*Read by title before the forty-third annual meeting of the Florida Medical Association at Arcadia, May 10-12, 1916.

formerly unaccountable sorts of development.

One curious freak of change I found reported by an investigator living in Europe. A woman in advanced life, having passed the climacteric change, was seen to lose her female characteristics and to take on those of the male. She became muscular and came to enjoy heavy outdoor exercise, grew a beard, acquired a heavy voice like that of a man; in short, she became masculine in many particulars. Later, when examined in autopsy, the chief mark of tissue change observed was a lipomatous degeneration of the suprarenal capsules. In the light of the new physiology the changes described in this woman may have resulted from unbalanced hormones.

Another evidence of the transforming power of the internal secretions is furnished in the experimental work I saw reported by Eaton of Seattle. "Upon the removal of the ovaries of a young female, followed by the transplanting of the sexual organs of the opposite sex, the female was caused to develop into an individual having all the characteristics of the male." "There are well authenticated cases in which the decidual tissues during pregnancy have developed in remote organs as well as in the uterus, showing that the development of the placenta is but one of the local manifestations of a general condition, and this (condition) is brought about and controlled by the secretion of the ovary."

Here I might mention the case of the Polish sisters, the report of which fell under my notice some months ago. These twins were born attached to each other back to back, the connection being similar to that of the Siamese twins so well known in this country a generation ago, the same blood circulating through the bodies of both. When they reached maturity, one of them was married, and in the course of time a baby was born. The galactogenic function of the breasts of both sisters was immediately activated. Both the mother and her twin sister gave milk. This fact is interpreted by physiologists as teaching that, being supplied with blood common to them both, the breasts of the virgin sister were activated by the hormone generated in the uterus (perhaps by the placenta) which nature intended for the breasts of the mother alone. However conservative and doubtful we may feel inclined to be, we cannot deny that the theory our physiologists offer furnishes a rational explanation of the phenomenon observed.

Among the most prominent of the teachers giving out these facts and opinions may be mentioned Ott, Simpson, McCallum, Klotz, Beebe and Sajous. Indeed, the literature of this new physiology in America has become so voluminous that the ordinary student cannot hope to examine it all, while in Europe, a system of therapeutics based upon these teachings has been developed until it has become quite general. Opotherapy, as the French generally call it, is said to be much more commonly used in Europe than it is in this country. In Harrower's new book, "Practical Hormone Therapy," we have an admirable compilation of much that has been taught, already classified and tabulated.

In the last decade of the nineteenth century we thought we had wonderful light in the definite, clear and startling revelations of truth concerning the activities of the peptic glands, brought to us in the English translation of the works of Pawlow, the Russian scientist, and we had. Though they were novel, and, at that time, unique, I have never heard their correctness called in question. In the higher and better form of therapeutics springing from a knowledge of digestion in health and disease, namely, in dietetics, the teachings of Pawlow and his fellow investigators have done much for science, and, hence, for humanity. But still more wonderful and more intensely interesting are the facts brought to us in the revelations given concerning the system comprising the various glands producing hormones.

Pawlow told us that the peptic glands seem nothing short of purposive in their activities, and so definite in their action that each varying kind of food employed calls out a special quality as well as a definite quantity of gastric juice, and always the same in all healthy animals, under the same given circumstances.

The new physiology teaches us that all the varied functions of all the organs of the body are under the direct control of these chemical messengers or hormones, manufactured in some distant organ and furnished at just the right time and in the needed quantity to make for the good of the animal economy. They tell us these hormones are furnished in pairs or in groups which antagonize each other. As muscle antagonizes muscle in the motor system, thus securing co-ordination in the movements of the various members, placing all under the control of the will, so these hormones antagonize one another in their effects, giving co-ordination of function throughout the body. For example, the thyroid hormone tends to stimulate the heart to more rapid action. One of the various symptoms of hyperthyroidism is tachycardia or rapid heart action not necessarily associated with fever. We have evidence that in the blood of those whose thyroids have been removed there is a chemical substance which retards the action of the heart. Under the influence of these antagonizing forces the action of the heart in health may be held under control.

Again, adrenalin, one of the hormones of the suprarenal capsule, is believed to stimulate the glycogenic function of the liver, while a hormone produced in the pancreas inhibits this function. While these two agents are acting together in the healthy, the amount of sugar manufactured is just enough for the system. When these hormones are unbalanced, ill health follows, one manifestation of which is diabetes, or an excess of sugar in the system, giving glycosuria.

Pawlow's teachings suggest that the Creator is a Physicist and a Phychologist. The new physiology teaches that He must also be an all-wise Chemist, for the organs producing these wonderful chemical substances now believed to be essential to the co-ordination of the activities of all the organs of the body—these organs, I say, mutely declare in accents loud and clear, "The hand that made us is divine."

As the kidneys are known to be complementary to each other in the performance of their common excretory function, either organ being able to take up more than its usual amount of work, in order, to some extent, to assist the other when injury or disease makes it necessary, so some of these hormone secreting glands seem to be complementary to each other. Two or three of them sometimes share together the work of activating or inhibiting the activities of certain important organs. Thus the vaso-constrictor action of extracts made from the suprarenal gland, and of those from the posterior lobe of the pituitary gland, are similar, the latter being credited with much more permanent effects.

Some enzymes are also hormones. We are all well acquainted with the common use of hydrochloric acid as an aid in certain forms of indigestion, having been taught nearly a generation ago that it acts in the digestion of proteids. Now we are taught, however, that as soon as the hydrochloric acid, either the natural ingredient of the gastric juice or that furnished artificially passes through the pylorus and comes in contact with the mucous membrane of the duodenum, secretin is produced in increased quantity. Carried in the blood stream, this soon reaches the pancreas which it immediately activates to produce the enzyme trypsin, the richest and most energetic of all the ferments of digestion, and is the pancreatic agent in the reduction of proteids. What actually takes place, we are told (and this I have in a personal letter from Harrower), is this: The secretin

releases the trypsinogen which it changes into trypsin under the influence of the so-called "ferment of ferments—enterokinase."

We are told also that this same enzyme trypsin may also act as a hormone, stimulating metabolism in distant parts of the body, securing increased growth or storing up fat.

Nothing could be more fascinating, from a physician's viewpoint, than the therapeutic application of these principles and facts. Much good work has been done by many clinicians in this field of investigation, and some applications of organo-therapy, being found dependable, have become popular in the profession; yet much remains to be done. What doctor has not used adrenalin locally as a vaso-constrictor and pituitrin in his obstetrical practice?

Although the physiologic antagonism between the mammæ and the pelvic organs has been suspected or believed for a long time, it was not fully established as a fact until the "hormone theory" was brought forward and substantiated.

As early as 1896 Bell began treating uterine fibroids with thyroid extracts. Later he substituted mammary extracts with very encouraging results.

In cases favorably reported pain and hemorrhage disappeared or were diminished, while in others the tumors were materially diminished in size. The reports of Shoberg are quite as favorable, and mammary extracts are strongly recommended in both menorrhagia and metrorrhagia. He states, however, that an addition of a small amount of thyroid extract insures even better results.

More recently Feodoroff has published statistical reports of the use of mammary extracts in the treatment of uterine fibroids. In 53 per cent of his cases, he was able to note a reduction in the size of the tumors. In 83 per cent, hemorrhage and profuse menstruation were absolutely controlled. In 40 per cent, pain was abolished, and in only 14 per cent of his cases was there total failure.

Mekerttschiants reports fifty cases personally treated, and he is enthusiastic in his praise of the method. He regards it as "the touchstone" of all uterine fibroids before operative interference is decided upon.

Some of the cases of uterine fibroid that come to us are inoperable, while others, either from fear of the knife or from poverty, do not reach the surgeon. A method that offers such a large proportion of improvements is certainly not to be ignored; moreover, these reports show that the general condition of cases that must ultimately come to the operating table have their condition vastly improved by preliminary mammary treatment, thus giving better end results.

Both Nathan and Delaney have reported either marked improvement or entire cure of the cases of rheumatoid arthritis which they have treated with thymus gland extracts.

When a child is found not to have enough antibodies in his tissues to resist the poison of diphtheria germs, or of tetanus germs, we do not hesitate to ask the horse for antitoxin that more antibodies may be generated, and we freely furnish it to the child, thus cutting short his sickness or, perhaps, saving his life. So, likewise, there should be no prejudice against asking the sheep or cow for a supply of secretin for indigestion, or of mammary gland extract for hemorrhage caused by uterine fibroids, or of the thyroid glands when the patient shows any one of the vast number of symptoms of hypothyroidism.

In view of the large amount of clinical study that is being devoted to this subject, may we not expect to see the application of these principles become much more common, and in consequence, to see the healing art become more natural, hence, more scientific?

The past twenty-five years has witnessed a marked change in the esteem in which

internal medication is held by both medical men and the more thoughtful portion of the laity. Professional men are viewing with favor the strong trend toward dependence upon natural therapeutic measures rather than the exhibition of poisonous drugs. Hygienic therapy is far more popular now than it was a generation ago. Since hormone therapy is, strictly speaking, a drugless method of healing disease, its appearance just now seems quite opportune.

In the past few years improvements in the methods of surgery and successes achieved through bacteriological investigations, have enjoyed the limelight of popular attention. The internal secretions seem now to be demanding their share of recognition from all who care to keep up with the march of human progress.

THE DUTY OF THE PHYSICIAN TOWARD THE ERADICATION OF MALARIA.*

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It is generally recognized by both the laity and our own profession that while in the past all that was expected of the physician was the curing of ills and the giving of relief to the sufferer, today more is expected and even demanded of him by civilization. As our knowledge concerning the etiology and transmission of disease has increased, so also has our ability to be of service to mankind not only in recognizing and treating disease but in actually preventing it. We also recognize both in surgical and medical fields that properly applied management of our patients is in itself a potent factor toward the betterment and progress of civilization.

In surgery the American Society for the Control of Cancer, an organization including the most brilliant surgeons within its ranks, is carrying on a propaganda of education, having foremost in mind the necessity for early recognition of this dread disease, recognizing that in an early recognition lies the most formidable weapon in cutting down the mortality that now numbers many thousands each year. The surgeon of today realizes that his duty is not limited to the actual operative field, but immense as his opportunities may be in his field of endeavor they do not compare with those offered the medical man. We have only to stop and think of the measures we now have at our command, to say nothing of further measures which as a result of intensive research work we have good reason to believe may soon further replete our armamentarium, for the control of such diseases as smallpox, typhoid fever, tuberculosis, diphtheria, yellow fever, poliomyelitis, uncinariasis, the dysenteries, malaria and many others, to thoroughly appreciate our opportunities and responsibilities.

Take any portion of the civilized world today and compare the morbidity and the actual mortality of any of these diseases with that of even a decade ago, and medicine has surely a monument that every physician should be proud of. We have, however, not done enough, and in addition to the work being carried on by the sanitarian, in addition to that carried on by the various educational bodies, the physician has a distinctive duty in helping not only to reduce but to actually exterminate certain diseases still responsible for a large morbidity in various sections of the world, resulting in untold misery and hundreds of thousands of preventable deaths. Among the foremost of these is malaria. I cannot emphasize too strongly that in my opinion the greatest duty the physician has today, especially the southern physician, is the actual extermination of this disease. In the consideration of the subject it must be remembered that in determining the etiology—the transmission from mosquito to man and again from man to mosquito, research workers have completed their work to the minutest detail.

*Read by invitation before the Columbia County Medical Society at Lake City, November 6, 1916.

Again let us realize that we have in the salts of quinine an absolute specific for fighting these infections. Should we not, with this knowledge, put our shoulders to the wheel and eradicate an infection that is the cause of so much misery, suffering, innumerable deaths and of such enormous economic loss to both capital and labor? How can we as physicians apply our knowledge to the eradication of this infection?

Volumes have been written, and fortunes spent, toward the sought-for eradication with mosquito extermination as the theme, but, while not wishing in the slightest to detract from the work of our sanitarians in mosquito extermination for the control of malaria, I maintain that in countries where you can only control the mosquito you can only control malaria. On the other hand I claim it is practical in temperate climates not to be satisfied with the control of malaria, but that with the working knowledge we have of the cycle of the parasite in man and the mosquito we should not be content with anything less than complete eradication. Carrying on a campaign for the eradication of malaria by mosquito control is to my mind very similar to treating a population suffering with uncinariasis by feeding them on thymol, but making no provision to furnish them with shoes or sanitary privies. How then should we approach this task? In answering the question, let us review the cycle of the malarial parasite, considering first the asexual cycle as it takes place in the human host, then the sexual cycle as it occurs in the body of the mosquito, and finally the effect of early diagnosis and the administration of proper specific treatment on this cycle, demonstrating as we will that the evolution can be broken at any point during the cycle in the human host.

We have four distinct species of malarial organisms known as the Plasmodium vivax producing benign tertian infections, Plasmodium malariæ producing quartan infections, Plasmodium falciparum producing æstivo-autumnal infections of the tertian type and Plasmodium falciparum quotidian producing æstivo-autumnal infections of the quotidian type. The general principles of evolution are, however, the same in all species, although there are differences in the morphology of the parasites and the time required for the complete asexual cycle, depending upon the specie.

A person bitten with an infected anopheline has injected into his circulation during the biting process by this insect numbers of minute organisms known as sporozoites, these being contained in the saliva of the insect. They are needle-shaped forms which immediately upon gaining access to the circulation of man penetrate the red corpuscles, the parasites taking the red cells as their habitat during the asexual cycle. Immediately upon entering the red cells, the sporozoites assume ring-shaped forms and are known as trophozoites. These organisms are first nonmotile, they assimilate hemoglobin from their host and rapidly become actively motile, developing pigment as they grow. These ring forms or trophozoites vary both in size and morphology depending on the various specie. They later lose their ring form and take on various shapes and are known as schizonts. Still actively motile, they increase in size gradually enroaching on the red cell they occupy until the presporulating form is developed. As the sporulating body develops, numerous ovoid bodies are to be seen within the parent organism. As sporulation is completed, the red corpuscle is destroyed and the numerous ovoid bodies known as merozoites become free in the blood plasma. They immediately penetrate other red cells and are ready to continue the same process of evolution originally started by the sporozoites or the minute bodies injected by the mosquito in her biting process. Thus the evolution goes on *ad infinitum* until arrested by specific treatment, by the natural resistance of the patient, or until evolution takes on a peculiar phenomenon in which the merozoites,

instead of continuing the asexual cycle, undergo a morphological change and develop into gametes or sexual organisms, the male being known as the microgametocyte, the female as the macrogamete.

While every step of the evolution just described has been observed by innumerable authors, as has also the sexual evolution taking place in the body of the mosquito, to be later described, we have no definite knowledge as to the cause or causes that results in a merozoite ceasing the asexual cycle, and assuming that resulting in the formation of gametes, which upon being ingested by the biting mosquito undergo the sexual cycle in the body of that insect. We do know, however, that these forms are never seen until an infection is at least ten days old, that they are never seen in a case that receives prompt, efficient and continued specific treatment and that inadequate treatment consisting of small doses of quinine or single large doses, in other words, that any other than intensive specific treatment tends to develop these sexual forms. The sexual forms being less amenable to quinine, the theory has been advanced that when the cycle seems threatened either by the natural resistance of the patient, or by the introduction of quinine, insufficient to destroy the plasmodia, but enough to sound, as it were, a note of warning—that the merozoite scenting danger and the interruption of the cycle cries "safety first" and the phenomenon of the formation of gametes is under way. The malarial carrier presents a more or less well-known clinical picture to all of us. More or less frequent exacerbations of fever is the rule, but an important consideration is the fact that an individual may harbor gametes without suffering any apparent inconvenience. While it is true that their hemoglobin content will be below normal, a gamete carrier may remain in fairly good health for long periods of time, but is, of course, a source of infection to all anopheline mosquitoes that feed on his blood. An important feature in an educational propaganda for the eradication of malaria is to disabuse the minds of the inhabitants of an infected territory that their recurrences of malarial infection are to be taken as a matter of course and to educate them up to the point of appreciating the fact that in allowing themselves to remain chronic sufferers of the disease they are themselves perpetuating the infections in harboring within their circulation the sexual forms of the parasite. It should be clearly understood that macrogametes and microgameocytes once formed are incapable of continuing evolution within the circulation of man, and that, although they remain alive for long periods of time, actual evolution cannot proceed until these organisms reach the stomach of the mosquito.

Let us now consider the further evolution of the organism as it occurs in the body of the mosquito. The insect feeding on a carrier, gametes are ingested during the blood-sucking meal. The first change noted occurs in the male organism, the microgametocyte, and consists of long thread-like filaments being thrown out, these number from two to eight in number and measure in length from two to four times the diameter of the parent organism. This process of evolution is termed exflagellation. The thread-like filaments are seen to thrash about and to finally detach themselves from the parent body which undergoes degeneration. The filament described is the full-grown male or microgamete, which now seeks, penetrates and fertilizes the female form — the macrogamete. As a result of fertilization an oval body becomes formed, known as a zygote. As evolution proceeds within the muscular walls of the stomach of the mosquito the zygote loses its oval shape and becomes an elongated form and is termed an ookinette. As evolution further progresses, this in turn becomes the oocyst, having a diameter about 7 microns. Within this organism sporozoites develop which finally find their way to the salivary glands of

the insect, a complete cycle of evolution being thus terminated, and we find the insect ready to again transmit sporozoites in her biting process by which the endless chain of evolution can be carried on.

Of especial significance in considering the eradication of malaria in all temperate climates is the fact that it has been demonstrated that the cycle within the mosquito is interrupted during the winter months. A temperature of 60° Fahrenheit kills all forms of the organism within the body of this insect, which means that with the advent of warm weather all mosquitoes are sterile until such time as they are able to feed on infected man in whom the asexual cycle continues regardless of climatic conditions. With as complete a knowledge as we have of this evolution, it is hard to understand why for so many years so much stress has been laid upon the fact of mosquito infecting man, with so little attention being drawn to the plainly evident fact of man infecting the mosquito. It is an interesting fact that not only does man infect the mosquito, but to a great degree regulates the intensity of infections the mosquito is capable of producing. By that I mean a mosquito biting an individual only moderately infected with gametes develops sporozoites in such numbers as to be capable of producing only moderately severe infections, while on the other hand, let a mosquito feed on the blood of an individual carrying large numbers of gametes in his circulation, the insect develops sporozoites in such numbers that when she feeds on another person large numbers of these minute organisms are injected and an intensive infection results.

With such complete knowledge of the life cycle of the malarial organism in both man and the mosquito, bearing in mind that at least in temperate climates the cycle is broken within the body of the mosquito during the winter months, having an absolute specific in the salts of quinine for the interruption of the cycle in man, how can we best proceed to exterminate the disease?

It is not my intention to discuss the many measures we have at our command or to even follow the line of discussion generally followed in considering the eradication of malaria other than to mention them in passing. Briefly they may be summed up as mosquito destruction by physical means, such as drainage, filling in of lowlands, the actual destruction of mosquitoes within the home by fumigation or other means, the oiling of water containing larvæ or the use of chemicals for the destruction of larvæ, mechanical means for the prevention of the infected mosquito gaining access to man and the general education of the public concerning all measures employed for the control of the infection.

Each and all of these have their place in a well-regulated campaign against malaria; the adoption of these measures, however, belong more properly to the sanitarians and health officers than to the general physician. There is, however, an important measure that I feel has been largely neglected in campaigns for the eradication of malaria, a measure which neglected makes it impossible for most campaigns to be fully effective, a measure that directly concerns the man engaged in the practice of medicine. I refer to measures directed against the plasmodia within the circulation of man. When we consider the asexual cycle of this organism as it occurs in the circulation of man, when we recall that gametes do not form until after infection is several days old, when we realize that without the formation of gametes the infection of the mosquito becomes impossible, thereby breaking the cycle, when we recall that the cycle is broken in the body of the mosquito under certain climatic conditions, when we stop and consider that the early diagnosis and administration of effective treatment not only cures our patient, but renders the infection of other mosquitoes an impossibility, must we not recognize how grossly we err

in our duty toward mankind when we fail to adopt these principles? The question is raised what constitutes effective treatment against malarial infections. While laurels may be heaped upon the crowns of members of our profession for many good deeds performed, I feel that it is to our shame that this question cannot be answered beyond cavil and quibble. Select at random a dozen members of our profession and you will find advocated as many lines of treatment. I do not refer to the small minority who advocate treatment other than with the specific, quinine, but, knowing that in this drug we have a specific, I believe the greatest duty the profession owes to itself and to mankind is to standardize the treatment of this disease. Is there any great amount of quibbling as to the dosage of mercury and salvarsan in the treatment of lues? Why cannot we have a standardized treatment applicable to the cure of malaria? In closing I would urge upon you the necessity for an early diagnosis of the disease, for the administration of continued specific treatment for at least six weeks and the treatment of all carriers during the winter months so that with the advent of spring there are no latent infections upon which the mosquito can feed and become infected.

VITAMINE.*

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(*An abstract of an article entitled, "Concerning Oryzanin, a Constituent of Rice Bran and Its Physiologic Importance," by Suzuki, Shimamura and Odake, which was published in the Biochemische Zeitschrift, number* 43, *in* 1912.)

Eijkmann, in 1897, observed for the first time that fowls fed exclusively upon rice, which had been carefully freed from its "silver skin," in a short time lost their appetite and died under strong starvation. He further particularly remarked that these appearances have a great similarity to beriberi in man. If the fowls are fed with unpolished rice, or with polished rice and rice bran, they not only live but those which had become ill were rapidly cured. These observations were later tested by various writers and clearly established.

Concerning the preceding facts no satisfactory explanation was forthcoming, but various ones differing widely were offered. According to Eijkmann we have here poisoning through poisonous material in the starch of polished rice, or poisons produced through enteric fermentation of the starch, or through abnormal metabolism in the animal. According to Maurer, the illness is a poisoning due to fermentation products formed during digestion, particularly oxalic acid. Shakaki believed the illness resulted from poisonous materials produced by bacterial activity in the rice itself. Matsushita believed the trouble was due to a deficiency of albumin, and Schaumann to a deficiency of organic phosphorous compounds. The history and literature of these observations may be found in the "Bulletin of the Japanese Ministry Commission for the Study of Kakke (1911)."

The only certainty was that rice bran contained some material which had the property of curing the sickened animals or of preventing the sickness. The authors worked on this subject four years; first verifying Eijkmann's observations and then isolating the active material from the bran and studying its chemical nature. The ethereal extract of rice bran is inactive, but the fat free bran remaining is equally active with the original. If the fat free bran be extracted with hot alcohol, then the active material is found in the alcoholic solution and the residue is completely inactive. Since polished rice is very deficient in inorganic constituents, such as phosphorous, iron, calcium, magnesium, potassium, etc., the

*Read at special meeting of the Volusia County Medical Society held at the Ormond Hotel March 21, 1916.

authors surmised that the animals were suffering from a lack of mineral matter. This assumption, however, could scarcely be correct since the residue after extraction with ether and alcohol while inactive is still rich in albumin, starch, fibre, pytin, salts, etc. They clearly established that casein, peptone, egg albumin, lecithin, phytin and salts have no protective or curative action against the illness.

The alcoholic extract consists of an acid, thick, brown syrup, very rich in sugar, organic acids, lecithin and salts. When this is dissolved in a little water, weakly acidified with sulphuric acid and precipitated with phospho-tungstic acid, there results a flocculent precipitate that carries with it the major portion of the active material; while sugar, organic acids and other impurities for the most part remain behind in solution. The precipitate is then decomposed with barium hydroxide and a weakly acid, clear brown syrup is obtained that is ten times as active as the alcoholic extract. The authors call this "Raw oryzanin 1."

Raw oryzanin 1 is then dissolved in a little water and precipitated with tannin. Part of the oryzanin is precipitated. The tannin precipitate is decomposed by barium hydroxide and the excess of barium is separated by sulphuric acid. There results a clear brown syrup—"Raw oryzanin 2"—which is three times as active as raw oryzanin 1. A fairly pure precipitate can be obtained by direct precipitation of the alcoholic extract with tannin. From raw oryzanin 2 the authors, by means of picric acid, isolated the active material, oryzanin, in a fairly pure state. The picrate yield is very small and there are some doubts concerning its exact chemical composition.

One-half to one centigram of the picrate preparation per os or subcutaneously to a pigeon sickened through an exclusive diet of polished rice effects a cure in a few days; the appetite rapidly returns and body weight regularly increases. A pigeon can be kept alive at desire if the same dosage of oryzanin is given daily with a polished rice diet. In the absence of this the animal dies in two or three weeks. A pigeon weighing 300 grams eats 25 to 30 grams of rice daily; the oryzanin constitutes about 1-5000 of the total amount of food. It is remarkable that so small a proporttion of oryzanin exercises such a large influence on the nourishment of the animal. The question then arises as to other animals. The authors found that fowls, mice and dogs react toward oryzanin exactly as pigeons do. Mice die surely in ten to fifteen days upon an exclusive diet of polished rice, but remain healthy and normal for a long time if the alcoholic extract of bran or raw oryzanin is also given. Dogs fed cooked rice and boiled out horseflesh experienced no trouble at first, but in two or three weeks the appetite failed, and after five to seven weeks they died under strong starvation. 3 or 4 grams of the alcoholic extract, or 0.3 to 0.4 grams of raw oryzanin 1 cured apparently morbid dogs in a few days; the appetite rapidly returned and the body weight quickly increased. Withdraw the dosage of oryzanin and the animal becomes sick again. With growing dogs we have in seven months repeated four times the same course of events. Fats and salts show no observable influence and we take it that oryzanin constitutes a material essential to the maintenance of animal life. With pure albumins, fats and carbohydrates and salts as a diet, animals cannot remain alive for long. Such a diet does not contain oryzanin. To investigate further, we have fed pigeons and mice with a food mixture of pure isolated foodstuffs put together. Two pigeons were fed with potato starch, peptone, lecithin, phytin and salts; two others were fed the same way with the addition of three centigrams of raw oryzanin 1. The difference was remarkable; the two former died from starvation in ten to fifteen days, while the other two remained healthy and notably increased in weight. Instead of peptone we

have used casein, egg albumin and bran albumin (extracted by dilute alkali and precipitated by acetic acid) with results exactly as before. Other pigeons were fed on an albumin free diet. They naturally could not live long, but those pigeons which received oryzanin lived three times as long as those without oryzanin. The daily loss of weight in the first case was three times as great as in the latter.

The exact role of oryzanin in the animal organism is unknown, but it is entirely clear that without it animal life is impossible, at least, for fowls, pigeons, mice and dogs. It may be noted that various authors have reported a variety of researches in an endeavor to sustain animal life for a long time on a diet of a mixture of pure foodstuffs. Most report failure, but Rohmann and Osborne have recently had somewhat better results. We must never overlook the influence of oryzanin, and Rohmann and Osborne would have obtained still more satisfactory results if oryzanin had been present in their mixture of foods.

Wheat, barley, bran, beans, millet, oats and green vegetables are able to preserve life in animals. It is not certain whether the active material in various food substances is always identical with oryzanin from rice bran or whether they constitute a class of substances. Milk, eggs, fish and horseflesh, as such or the alcoholic extract thereof, have shown little or no activity toward pigeons, but toward dogs and mice the behavior was somewhat different. The alcoholic extract of horseflesh was as active toward dogs as was oryzanin, but was found to be somewhat less favorable to mice. It is possible to keep mice healthy more than fifty days by feeding on polished rice with the addition of the alcoholic extract of horseflesh. An alcoholic extract of milk is also capable of maintaining mice healthy more than fifty days, while the residue is completely inactive.

Results summarized:

1. Fowls, pigeons, mice and some other animals when fed exclusively on polished rice steadily sicken, suffer profound loss of weight and finally die. These results are caused by the absence of a material in the polished rice that is absolutely necessary for the maintenance of animal life.

2. This indispensable material has been isolated in the pure state from rice bran and the discoverers named it oryzanin. Oryzanin plays an entirely special and quite as important part in the maintenance of animal life as albumin, fat, carbohydrate and salts. Without oryzanin the other materials named can exercise no physiologic function.

3. Every food which lacks oryzanin cannot support animal life for a long time.

4. Artificial food mixtures from albumin, fat, carbohydrates and salts without oryzanin cannot maintain animal life for a long time.

5. Dogs cannot exist upon boiled out meat and polished rice, and are completely starved after three to four weeks, but if the so-starved dogs receive 3 grams of alcoholic extract of rice bran or 0.3 grams of oryzanin daily, they are quickly restored.

6. The distribution of oryzanin in various foods is rather general. Since, however, polished rice in certain countries, as Japan, constitutes the chief food of the common people, it may often happen that a lack of oryzanin may have serious results, and this may also be true in prisons, armies, ships, etc., should the diet chance to be oryzanin free.

Addenda.

Decomposition products of raw oryzanin: Dilute mineral acids or alcohols readily decompose oryzanin, causing it to lose its peculiar properties. Oryzanin is a very unstable compound, and among the products of the decomposition of oryzanin the investigators identified an acid which they called Alpha, $C_{10}H_6O_4$, and another which they called Beta, $C_{18}H_{16}N_2O_9$. These yield the Diazo reaction, indigo coloration with phosphomolybdic acid and ammonia, and decol-

orize blue starch iodide solution. In addition to these two acids are found cholin and grape sugar, together with nicotinic acid.

Phytin belongs to the plant kingdom. It is a magnesium and calcium compound of inosite and phosphoric acid. Inosite has the formula, $C_6H_{12}O_6+H_2O$. It is not a carbohydrate, but a hexa-hydroxy-benzene, $C_6H_6(OH)_6+H_2O$. It is found in the muscles, liver, spleen, lungs, brain, suprarenals and kidneys.

TREATMENT OF THE MORPHINE HABIT.*

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Morphinism is by no means a simple disease, on the contrary, it is one of the most complex with which the practitioner has to deal.

Two questions concern us primarily when a morphinist presents himself for treatment. Is this person a fit subject for treatment? What method should be used? Too much emphasis cannot be laid upon the necessity of making a thorough physical examination of the morphine habitue before he is subjected to the withdrawal of the drug, or to the severe treatment necessary to promote this object. Cancer with pain or any intense pain that will be present after the desire for morphine has been removed, precludes the necessity for treatment to remove the habit. Old age with its degenerations, and myocardial degeneration at any age also preclude all strenuous treatment in the effort to overcome the habit. It should not be understood, however, that these patients should be allowed morphine ad libitum, for it is well known that these patients will, if allowed, take more than is necessary to relieve pain. It has been my practice to allow them a definite amount of the drug to last for a given period. It is given in combination with belladonna, nux vomica and cascara. In this way the patient gets a minimum amount of morphine, together with other drugs that the physician may see fit to give. The quantity can easily be kept at a minimum, and therefore mental deteroriation is less likely to occur.

Occasionally we see cases which can be entirely cured, where in the beginning it is least expected. The following case is illustrative: J. T. S., white male, age 65, widower, came to my office July, 1911. Complaint: Shortness of breath, cough, weakness and swelling of feet and ankles. Careful questioning elicited the facts that he had taken morphine for 25 years; began using it for relief of rheumatic pains, was taking 8 grains daily by mouth. Physical examination showed apex beat displaced to anterior axillary line in sixth interspace, systolic murmur at apex transmitted to axilla. Liver dulness extended two finger breaths below costal margin. Marked edema, of feet and ankles. I persuaded this patient to take his morphine in liquid form. I gave him his usual amount in combination with belladonna, nux vomica and cascara, also gave 20 minims of tincture of digitalis 4 times a day for several days. A reduction in the morphine was carried out over a period of two years until patient was finally cured. This case illustrates the necessity for care in selecting a method of treatment for each individual case. One of the rapid withdrawal methods of treatment would certainly have resulted disastrously. I am also lead to believe that had he continued the use of large doses of morphine disastrous consequences would have ensued.

Dr. H. E. Goetz, in a recent article in the *Journal of the A. M. A.*, calls our attention to the fact that degenerations of the kidneys, as Bright's disease, are a serious complication to contend with in attempting to treat the morphine habit. Certainly any acute inflammation of the kidneys would contraindicate the treatment. Also it should be recognized that if the elimination of the

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kidneys is interfered with by disease, all eliminative methods used in the treatment will not be as effectual as when the kidneys are healthy. However, it must be borne in mind that nephritic morphine habitues are constantly aggravating their kidney condition through elimination of toxines produced by the improper metabolism which results from the prolonged use of morphine, and since most of the elimination in these treatments is carried on through the bowel, the danger and difficulty in withdrawing the morphine from nephritics is probably not very great. It must be urged, however, that a very gradual reduction with tonics and eliminants is better than the method of rapid withdrawal.

The most popular treatments at present are the Townes-Lambert treatment, the Pettey treatment, and the Sceleth treatment. Dr. Alexander Lambert described his treatment in the *Journal A. M. A.*, September 25, 1909. The treatment consists of the administration of compound carthartic pills and of blue mass to produce free catharsis and relieve congestion and inactivity of the liver. The other medicinal treatment is a mixture of 15 per cent tincture of belladonna, fluid extract of xanthoxylin and fluid extract of hyoscyamus. This latter is given in ascending doses until signs of belladonna poisoning appear.

Dr. Geo. E. Pettey, of Memphis, Tenn., uses the following cathartic mixture:

Calomel.
P. Extract Casc., aa gr. 10.
Ipecac, gr. 1.
Strych. Nit., gr. 1-4.
Atroph. Sulph., gr. 1-50.
M. Ft. Cap No. 4.

One of these capsules is given every 2 hours. In addition to this cathartic mixture, he depends on scopolomine in 1-200 grain doses, and spartein in 2 grain doses for his medical treatment.

Dr. Chas. E. Sceleth, who is medical superintendent of the hospital of the House of Correction, of Chicago, uses the following mixture:

Scopolomine, gr. 1-100.
Pilocarpine, gr. 1-12.
Dionin, gr. 1-2.
F. E. Cascara, m. 15.
Alcohol, m. 35.
Water, 5i.

The dosage of the foregoing is varied, according to the amount of morphine taken. Before this mixture is begun, the bowels are emptied with salines.

The objects aimed at in the treatment of the morphine habit are to eliminate the morphine that may be retained in the different parts of the body, to stimulate the activity of all glands, especially the liver, and to combat the drug by a physiologic antidote, and while these objects are kept in view, to give the patient as much rest as possible and to support his circulatory system.

Severe prostration must occur with any rapid withdrawal treatment. For lack of time the technic of these methods will not be described. Suffice it to say that atrophine in some form is relied upon to combat the suffering entailed by withdrawal of the drug, while catharsis is carried to the point of tolerance. Too much stress cannot be placed on elimination. Morphine can be found in the urine of addicts as late as nine days after the last dose has been taken, and in the liver, brain and kidneys as late as fourteen days.

Sceleth very wisely says that if the cause which led to the development of the habit is still present after a cure has been made, these patients are likely to relapse; if the cause has been removed, the patients are generally permanently cured. Consequently, if the cause has not been removed, it should be a subject for the most careful therapeutic and, if necessary, surgical consideration.

As a rule it is necessary to have all patients who are to be treated for drug addiction in a hospital. In fact there are very few addicts who can be relied upon to cooperate in a gradual withdrawal treatment.

However, there are a few who will pursue the treatment to a successful termination.

When the Harrison law was first enforced, quite a number of addicts applied to me for prescriptions for morphine and cocaine. I have never prescribed one grain of cocaine to an habitue because, unlike the morphinist, the cocainist can get along without the drug, while the morphine habitue cannot be deprived of his dope without serious consequences.

Morphine habitues view with great skepticism the idea of being freed of their drug whether by gradual withdrawal or other method; therefore, it is essential to gain the confidence and cooperation of the patient before treatment is instituted.

It is certainly a fact that most drug addicts can be more successfully treated in an institution than as ambulatory patients. But for obvious reasons all addicts cannot or will not go to a hospital. Many of these I have treated in the following way: The patient is allowed morphine straight for a while to ascertain definitely how much is taken. After this is determined, he is given a two days' supply in combination with belladonna in a liquid form, with explicit directions as to how to take it. He is told to take a definite amount of the mixture at a definite time, e. g., a drachm at 8-12-4-8 daily. I see the patient every two days, and the amount of morphine is reduced, according to his condition. The belladonna plays a double roll. It lessens the desire for morphine, having a synergistic action, and also prevents the patient taking the mixture to excess, because of symptoms caused by excess of belladonna.

When this plan is followed, the physician can incorporate any drug in the mixture that the patient may need. Nux vomica is a valuable tonic and, being bitter, keeps the patient in ignorance as to how much morphine he is getting. Codeine or dionin is used with great advantage in these mixtures. Eserine also is a valuable drug. It contracts the pupil and favors peristalsis. As eliminants cascara and podophyllin are frequently used, also a dose of calomel about once a week.

There is a wide-spread belief among the laity, and even among the profession, that the morphine habitue should be treated by a definite formula—turn the crank, as it were, and cure the patient. Nothing could be farther from the truth. All morphine habitues should not be treated alike any more than should all pneumonia patients. We frequently see patients who will be cured by one method where another will fail. A writer in a recent issue of the *Journal of the A. M. A.*, referring to the treatments I have mentioned, very forcibly expresses my idea in the following words: "There is no halo, and there is no zodiacal sign, and there is no prayer that necessarily accompanies these particular combinations of drugs. It is largely the forcefulness of the men who carry out the treatment, and persistency in obtaining the object aimed at, through some antagonistic drugs, profuse purging and support of the patient through his trial.

The following is a summary of the cases of drug addiction that have come under my care. The results are not brilliant, but still encouraging:

Number of cases treated, 26.

Number of cases cured, 12 (gradual withdrawal, 6; rapid withdrawal, 6).

Number of cases voluntarily discontinuing treatment, 9.

Number of cases now under observation, 3.

Number of cases known relapses, 1.

Number of cases discharged for non-compliance, 2.

215 *American National Bank Building.*

HERNIOTOMY.*

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In presenting a paper to this body on the above subject, I desire to say that to attempt

*Read before the forty-third annual meeting of the Florida Medical Association at Arcadia, May 10-12, 1916.

to write on the various methods of operators and operations would be too extensive and tiresome a subject.

Moreover, I wish to say that I have nothing original to offer, for the only knowledge I may have is gleaned from the various authors of well-recognized surgical works. I will confine my remarks to the inguinal hernia of the oblique type, for it is the class of cases that we have to deal with more often than any other type. This hernia occurs in more than ninety per cent of all cases presenting themselves to the surgeon for relief.

Hernia is the protrusion of a viscus from its natural cavity, through normal or artificial openings into the surrounding tissue. To thoroughly treat hernia of any variety, we must be well acquainted with the anatomical parts that are before us. I know of no other operation in which the knowledge of the anatomy involved is so important if we wish to restore the patient to his normal usefulness and activity.

The sac is made by the pouching of the peritoneum, protruding through the internal ring in this variety: The sac is divided into a body, mouth and neck. The body lies in the canal; the mouth is the opening in the abdominal cavity; the neck, the portion between body and mouth. The neck of the sac lies external, to the deep epigastric artery and follows the course of the cord through the inguinal canal.

As to the cause of hernia: More males than females are afflicted with this condition, due probably to the former leading a more strenuous life than the latter. Others mention such causes as the following: Occupation, obesity, pulmonary affections, trauma and anything that will increase intra-abdominal pressure; also heredity is mentioned by some as a predisposing cause. In the diagnosis of hernia it is usually a very easy matter, particularly when we have swelling increased by coughing, lifting, erect position or in any manner of straining.

Reduction causes the mass to disappear; also by percussion we note either dullness or tympany, due usually to intestines or mesentery. Sometimes we are confused by an enlarged inguinal gland, but, if we remember in adenitis, we have tenderness due to infiltration of tissue with products of inflammation and at the same time not being able to reduce the swelling, along with a history of short duration, we will be able to probably eliminate hernia.

Other conditions that may confuse one are, hydrocele, variococele, cysts and saphenous varix, but with proper consideration of the usual cardinal signs and symptoms of hernia, we should not often make mistakes in diagnosis.

The prognosis of hernia without some means of interference either by palliative or radical treatment is not favorable for cure. The prognosis in radical treatment of this condition is exceptionally good, everything being equal, the percentage of mortality being from two-tenths to five-tenths per cent and upwards of ninety-five per cent cures. This brings us to the consideration of treatment of such cases. It is reputed that more than a million trusses are sold annually in the United States. This is a most important factor for our consideration, for it behooves us to educate the public that in selected cases, the radical treatment is practical, safe and conducive to a happy and unhampered existence so far as relates to the hernia. The treatment of deformity is divided into palliative and radical.

I will not dwell upon the palliative or truss treatment further than to add my condemnation for such management of a case when there are no contraindications for the radical operative relief, for such palliative measures seldom effect a cure except in the very young.

The only cases that I consider fair subjects for palliative treatments would be in cases of irreducible hernia in the very stout, cases of grave constitutional diseases and the very aged.

The radical treatment consists in remov-

ing the sac, transplanting or not transplanting the cord and in general re-arranging the parts best adapted for each and every case. The procedure that I use is the Bassini operation. There are other operations devised by different excellent surgeons, but I think that I may safely say that the above method is practiced more often with better results in most of the clinics of this country. As everyone knows that this method consists in the transplantation of the cord from its old to its new bed, hence I will not describe the technique.

In large scrotal hernia's one should always be careful to examine for the bladder. Frequently I have come near cutting the bladder by not being sufficiently inquisitive. I have also found the appendix adhered to the sac in some of my scrotal cases.

In regard to the suture material of this operation, I do not think that as much stress is laid upon this as there were at former times, due to the fact that absorbable suture material is more safely and easily obtained. Any absorbable 20- to 30-day catgut sutures are chiefly used. Without too much tension, correct approximation with absence of fibre straining and infection, the results should be all that is desired. I usually keep my patients in bed for three weeks, not allowing them off their backs for that time, as I wish to give nature ample time to repair and accommodate herself to her new surroundings. By so doing I give the patient the benefit of every possible recuperative power, instead of benefiting the surgeon's reputation of getting his patients out of bed quickly.

The sequelæ to a herniotomy may be as follows: First, wound may not unite by first intention. Second, diffuse general peritonitis may occur. Third, the reduced gut may become gangrenous. Fourth, the reduced gut may not resume its normal function, but still not be gangrenous, but injured. Fifth, the reduced gut may remain partially paralyzed for a few days and then return to functionating. Sixth, cases of acute mania may develop and sometimes prove fatal.

POLIOMYELITIS OR HEINE-MEDIN'S DISEASE.*

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In the hasty preparation of this paper I shall not attempt to cover other than certain aspects of poliomyelitis, scarcely touching on either the transmission of the disease or of its treatment. I have both quoted and copied freely from all of the current literature of the day, and the paucity of facts establishing the transmission of the disease, does not warrant one in entering into voluminous discussions which are in the current print, but which have not demonstrated anything valuable up to the present time, and literature of this kind fully covering the subject, I think, comes to the office of every physician almost daily through the mails from very reliable sources.

I am especially desirous of impressing the members of this society with the multiple forms of the disease so considerably dissimilar from the spinal type as to escape recognition, excepting when one is fully conversant with all the multiple forms.

I wish to give credit to the following writers and authorities from whose writings I have freely copied and quoted in this paper: Monograph Medicine, Alfred Gordon, Llewelln F. Barker, C. H. Burr, H. M. Elsner, M. Howard Fussell, James H. McKee, Wm. H. Wells, Wade H. Frost, of the U. S. P. H. S., and others.

The term Infantile Paralysis, or even Anterior Poliomyelitis, is to my mind not free from at least misleading suggestions, for certain palsies occur among infants and children which are in no way dependent upon the toxic virus Flexneria-Noguchii, while this virus produces many pathological

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changes other than those demonstrable in the giant cells of the gray matter of the anterior horn of the spinal cord, and again the infection is not by any means confined to infants and children, because both during epidemics and among sporadic cases the clinical picture is readily recognized and diagnosed in adults.

While the disease has long been prevalent in this country and abroad, yet much knowledge has been accumulated since the studies of Heine, of Connstadt (1840), who called it "Infantile Spinal Paralysis," following which Stumpell recognized cerebral paralysis which he concluded must have the same etiology as Heine's disease, while in 1890 the greater advance was recorded during an epidemic in Sweden by Medin, who recognized that while the spinal type predominated involving the anterior cells and lower motor neurons, also recognized Cerebral, Bulbar, Polyneuritic and peculiar Ataxic forms of the disease which seemed to be due this identical infection. Following this again Wickmann's studies of the epidemic in Sweden in 1905-06 further extended our knowledge through his demonstration of the existence of a meningitic form, and of a form following the course of Landry's paralysis and also the abortive form, which form in all probability may play a very definite role in the transmission and dissemination of the disease. Hence, to Wickmann is due the honor of founding the epideminology of the disease.

Charcot was probably the first to definitely study the pathological anatomy of the disease and demonstrate the changes in the anterior horn cells, whose investigations have been followed by a more intensive study of Landsteiner, Popper, Leiner, Wiesner, Levaditti, Romer, Flexner, Lewis and others, who are able to demonstrate a filterable virus which is capable of communicating the disease from one monkey to another, both by intraperitoneal injections of the macerated cord of an infected monkey and from the juices of the nervous system of an infected monkey after passage through a Bakefeld filter and injected into a healthy monkey, and also, finally, by culture in ascitic fluid agar media, with all of which you are already familiar.

Conclusions of the recent studies plus, of course, the already established findings of former observers, lead us away from the suggestion received from the term Anterior Poliomyelitis from the fact that much more damage is incurred from the same virus outside of or independent of the incident of the anterior horn cells, and were we to conceive the full picture of the disease as included under the term Heine-Medin's disease, we might be less liable to some confusion in diagnosis. The appearance of the paralysis is the first certain diagnostic sign accepted in sporadic cases, and without such laboratory apparatus and technic as is quite impossible to the general practitioner of the present time, little evidence is obtained of the blood and spinal fluid. We must, therefore, depend upon the clinical picture for the evidence upon which to make a definite diagnosis, and this clinical picture may be a very varied one in the multiple syndromes produced through the infection by this virus, as the later studies signify much more extensive pathological changes than the term Anterior Poliomyelitis implies; in fact, the evidence is quite conclusive that the involvement of the anterior horn cells appear more prominent because of the resulting paralysis, while the incident of their more extensive degeneration is probably solely due to the fact of their extremely rich blood supply, for a peculiarity of Heine-Medin's disease signifies an acute perivascular inflammation with lymphocytic infiltration, not in any way limited to the anterior horn cells, but prominent there as a rule, and involving also arteries and veins of the gray matter including both the posterior horns and the spinal ganglia in the nervous system. The lesions are described in the litera-

ture of the day as widely disseminated meningo-encephalomyelitis. The infection spreads through the perineural and perivascular lymph vessels. Flexner, Peabody and Draper, in their report on the visceral lesions of human cases, describe the swelling of the mesenteric lymph glands, of Peyers' patches as well as the solitary follicles of the intestines, and remark on the surprise that such a disseminated infiltrative lymphocytic inflammation, involving so many tissues throughout the body, should in the majority of cases give rise to a clinical picture simulating a "System Disease" of the spinal cord. Other authors (Tuley in particular) describe the regular enlargement of the superficial glands of the body, the tonsils, the thymus and spleen, with cloudy swellings in other organs. Fussell describes the morbid anatomy as follows: "The meninges are edematous and injected, the brain and cord appear also edematous, while the gray matter is swollen; the first changes in the meninges most noticeable on the anterior part of the cord is an acute interstitial meningitis, with small celled infiltrations about the vessels of the meninges and also minute hemorrhages. These cellular exudates, hemorrhages and edema dependent upon the vascular changes are the first effects of the virus preceding the nerve changes which are partly vascular; they may also be toxic and partly due to anemia."

If the hemorrhages and exudates are absorbed soon enough, the cells will regain their power, for the nerve cells either degenerate or recover.

The posterior root ganglia lesions are of constant occurrence and the histological changes are similar to those of the cord itself, which is an infiltration of the small round cells in the lymphatic spaces surrounding the vessels which enter the ganglia from the meninges, followed by a more general, diffuse exudation of the cells, with degeneration and necrosis of the nerve cells, and finally the entrance of the polymorphonuclear leucocytes into the necrotic cells and the removal of the disintegrating cells by neurophages. The suggestion has been made that these lesions in the sensory ganglia may in part at least account for pain which is such a constant feature in the acute stage of the disease, but another element in the production of pain is the cellular infiltration which is found along the nerve roots.

Fussell remarks: "The lymph glands and the tonsils are enlarged, the spleen often enlarges, the changes are much like those of typhoid fever; this is particularly marked in the liver. The disease must be regarded as a generalized process which effects parenchymatous organs, lymphoid tissue and more especially the nervous system."

Different authors and writers describe from five to nine distinct forms of Heine-Medin's disease, which appeal to me as a most potent factor in the recognition and diagnosis of the malady. The spinal form of all is said to be the most common and the most easily recognized, yet it may readily occur to one's mind that if the abortive form were or could be fully recognized in every instance that it might amount perhaps to fully or even over 50 per cent of the total cases occurring, for the abortive form either obtains without any recognizable symptoms, or there is the instance of natural personal immunity, which undoubtedly exists in certain individuals, against the Flexneria-Noguchii virus as there is against diphtheria and other similar infectious factors.

Following Romer, we recognize the following types in Heine-Medin's disease: Abortive, Spinal, Landry, Bulbar and Pontine, Cerebral, Ataxic, Polyneuritic, Meningeal, and still further Elsner recognizes and describes a chronic type.

Wickmann's statistics show 1,028 cases thoroughly investigated by him, of which 157 (15 3-10%) were of the abortive type, in which type the prognosis is universally

favorable. The toxins were either less virulent or the resistance of the patient higher or the infiltration does not progress beyond the stage of transient edema without destructive cell infiltration; hence, the lower motor neurons escape and there is no paralysis. It is further conceived and stated that there are probably many abortive cases without any recognizable symptoms whatever. Where there are symptoms, however, the most prominent are fever, pain in the head and back, very marked sweating, tonsillar invasion, bronchitis; these yield, however, after a few days or even less time, or there may be all the other manifestations of the prodromal stage of the more severe cases.

Mulier describes under the head of abortive cases those with a transitory paralysis of a single group of muscles, in which cases there may be evanescent loss of tendon reflexes. These he characterizes as "Rudimentary Poliomyelitis" and places the incident of abortive cases much higher than does Wickmann, stating that 50% is not too high a percentage of abortive cases during an epidemic.

The Spinal type is regarded as the most prevalent and especially characterized as the "Paralysis of the Morning," which is usually the first positive symptom upon which ordinary diagnosis can be affirmed, and many times is not suspected until the appearance of the paralysis. It is a complete motor paralysis, is flacid, may be extensive or confined to one or two groups of muscles, often irregularly distributed, may be as extensive as a triplegia, or even a quadraplegia, where two or more extremities are involved one usually suffers more than another, the peroneal and quadriceps muscles are oftenest involved and are the most liable to retain permanent injury, here the cranial nerves and the sphincters are rarely but occasionally involved. The sensory symptoms are due to the associated cellular infiltration of the meninges of the sensory branches and are usually of comparatively short duration. Muscular atrophy is the after-result due to the destruction of the cells controlling nutrition of the lower motor neurons, and in the unregenerated neurons soon appears the reaction of degeneration. This reaction, however, if present early in the case, does not preclude the possibility of final restoration of function. Its persistence after six to twelve months leaves no reasonable hope, however, of final recovery. Resulting deformities, kyphosis and scoliosis may be prevented by proper treatment, contractures remain, however, and can only be overcome by orthopedic treatment.

Landry type—There is a tendency among the leading neurologists of the day with the most extensive experience to feel that experience rather justifies one to conclude that Landry's ascending paralysis is identical with Heine-Medin's disease, there being another form of the disease. Of the first there is a characteristic ascending paralysis usually beginning in the lower extremities ascending and within a few days, three to five, involving the diaphragm, respiratory muscles, finally reaching the pneumogastric and glosopharyngeal nerve centers, producing spasm of the glotis, air hunger and death. Aspiration pneumonia is not uncommon among these cases, the majority of the patients die between the third and fifth day.

In the second form there occurs during the first twenty-four hours an ascending paralysis, the respiratory muscles being less involved and the pneumogastric and glosopharyngeal nerve escape, but the upper extremities are paralyzed before the end of the fourth day. The patient may live and continue paralyzed, but such cases are rare. Elsner reports one—a student who studied law entered the profession and made a brilliant success in spite of the persistence of a complete quadraplegia.

Bulbar and Pontine type.—Medin first described this form and it included the involvement of the cranial nerves in the motor

paralysis. Sometimes this is a concomitant with the spinal form, but this paralysis is more than apt to disappear within a few days or months—the facial is oftenest involved, the abducens and motor oculi are rarely included and very occasionally the optic nerve may be involved.

Cerebral type, Polioencephalitis.—This is really a mixture of the spinal form and an encephalitis dependent upon the disseminated invasion of this virus. The original description of this form was by Strumpell, whose observations have since been confirmed by Medin. This form included hemiplegia with well marked trophic changes in children. Developmental anomalies contractures, accompanied by the usual abduction of the arm, with flexed elbow, well marked clubfoot (pes equinovarus). The reflexes in these children are apt to remain abolished, in the adult they may be present or exaggerated, Babinski may be present or absent, in children athetosis may develop. Cerebral polioencephalitis may also involve the cerebellum and its paths, the paralysis due to this form may improve, but complete return of function is out of the question; children may retain their mental faculties, but go through life hemiplegics.

Ataxic form.—Medin, Wickmann and Zappert observed symptoms in some of their cases which after the prodromal period resembled Friedrich's Hereditary Ataxia. In these cases, the prognosis of any restoration of function is unfavorable.

Polyneurotic form.—These cases present all the features of a multiple neuritis, they are most apt to arise during epidemics characterized by a predominence of the more common forms of the Heine-Medin's disease and are affirmed by Medin to be due to the same virus which cause all other types; they are associated with sensory symptoms and tender nerve trunks, and frequently give evidence of meningeal inflammation, including Kernig symptom; the prognosis, however, of this form is usually very favorable, though the recovery may be slow.

Meningitic type.—This form of the disease presents early many of the symptoms of an acute leptomeningitis arising in the midst of an epidemic of Heine-Medin's disease, manifesting the Kernig symptom, followed by well-developed paralysis of the usual characteristics of infantile paralysis. Netter reports 29 per cent of his cases of the meningitic type.

And finally, there is described a chronic type by one or two writers as follows: There is a group of cases of unknown origin occasionally following trauma, in which there is a sub-acute or chronic paralysis closely resembling the spinal type of Heine-Medin's disease; these cases are found in adults without the acute period of the epidemic form and resemble, when fully developed, the spinal type of muscular atrophy. They differ from progressive muscular atrophy because of the early paralysis and the atrophy which follow it; there may be exacerbations during which further paralysis develop, involving separate groups of muscles in which atrophy follows, with the flacid paralysis. There is loss of reflexes and the reaction of degeneration.

In occasional cases there may be marked improvement of all symptoms. In a number of cases the exacerbations lead to progression of the atrophy and with ascending symptoms and increasing weakness and the patient dies. These cases represent degenerative processes in the anterior horns, and are often difficult to differentiate from progressive muscular atrophy, although as already mentioned, the early flacid paralysis offers a distinction; also the atrophic changes are secondary, never primary; the lower extremities are usually involved first, though there may be a monoplegia and later extension to other parts.

The prognosis is less favorable than in progressive muscular atrophy, for the disease when progressive ends fatally in from one to four years.

In conclusion, the point I want to make most clear is a competent picture of the multiple forms of the disease, so that they may be recognized as Heine-Medin's disease, and to distinctly impress each mind with the disseminated pathology concurrent in all forms, and again it is suggested by the most eminent writers of the day that the abortive forms which present few symptoms, if any, and no paralysis, or only transient paralysis, most likely occur almost exclusively among adults. It is not unlikely to be an important factor in the peculiar dissemination of the disease. One thing further in reference to the treatment—the leading neurologists are impressed with the necessity for continuous and continued rest for the paralyzed muscles —absolute rest for two, three or four months, after which may be used a light massage with electricity. These are the only facts which I think need to be especially mentioned, for so much as is known of the treatment valuable in those cases is included in the literature of all textbooks.

Townley Building.

ALCOHOLIC INSANITY, WITH REPORT OF A CASE.

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The effects of alcoholic drinks and the others they contain upon the nervous system of man are many and varied.

Besides the alcoholic deliria we have mental disturbances simulating a host of other conditions: mania-like conditions, melancholias, epilepsy, stuporous conditions, morbid impulses, progressive dementias, chronic persecutory insanity counterfeiting paranoia, etc.

The essential characteristic of all these is to be found in the progressive weakening of the mind.

The chronic alcoholic shows at the autopsy table the secondary degenerative effects of the drug in the wide-spreading arteriosclerosis, chronic thickening of the meninges, evidences of retardation of the lymph flow which have induced cirrhotic changes not confined to the brain, but invading organs essential to somatic life, the kidneys, stomach, liver and pancreas. The effects of this drug are not confined to the transgressors themselves but the results are passed on to the next generation in the form of lowered vitality, stunted growth, mental and moral imbecility, etc.

It is interesting to note the wide difference in the degrees of susceptibility to the influence of alcoholic drinks one meets with.

One man may stand a daily allowance of a quart for weeks and months before he is overtaken with mental and physical collapse; while his neighbor may have a violent delirium from a few glasses of beer or wine.

This difference is largely a question of the degree of stability of the nervous tissues, inherited or acquired.

Maniacal forms are more frequent than the melancholic, and most violent and destructive acts are sometimes committed while in this condition.

In alcoholic persecutory insanity, known as alcoholic pseudo-paranoia, the period of incubation may be short or a process of gradual evolution, and in this connection I beg leave to report a case now under observation.

M. J., 40 years of age, negro above the average intelligence. Had always been a moderate drinker with rare sprees. Father, mother and one brother died with some mental trouble. Has the usual superstitions of his race.

About three years ago he began to act queerly at times and imagined that fellow employees were working charms on him, so quit his job and remained at home and farmed.

Had headache, disturbed sleep and hallucinations of sight and hearing.

Several times drove rapidly home from his work in the field a short distance away, claiming to have seen people after him to kill him (the writer among them), and on

arriving home would call his wife to come to the gate to see them also. He often whistled in answer to whistles around him.

Thought people were trying to poison him through his food and several times came to the office for treatment for this.

People tried to poison him through his pillow at night, and he often smelled tobacco around the house, though neither he nor his wife used it.

Imagined people followed him around in the woods to get his money, but he always circumvented this by going a different way.

Always kept gun and shells by his bed for protection until they were taken out of the house.

Sees through plans people have made to encompass his downfall and imagined his lodge were all against him. Visions and hallucinations are always present and to a great extent of a sexual type.

The hallucinations and delusions foster irritability and roughness of manner and action whereas formerly he was quiet.

It is generally considered that this form of alcoholism is one of the most dangerous types of alcoholic insanity, yet so sane is he on every subject that he has twice fooled a court of inquiry into his mental condition by reason of the fact that they failed to get started on the right track in questioning him.

The course in these cases is progressive, the mental deterioration precluding any hope of recovery, and the treatment consists of isolation in an asylum until a terminal dementia ensues, at least.

PITUITRIN.

G. C. Kingsbury, M. D.,
Largo, Fla.

I was so elated in my recent experience with pituitrin that I consider it my duty to report these cases, hoping some physician and patient may enjoy the same benefit.

I was called November 29, 1915, to attend Mrs. M., and found a history of pregnancy at about five and a half months. She stated that on November 22d she noticed an unusual discharge which continued with some gradual increase, and becoming worse sent for me. I found three-fourth inch dilation, cord prolapsed and elbow presenting. She had had no pains at any time. At 2 p. m. I gave pituitrin and at 2:10 she had slight pains which increased in severity till 2:45, then moderate till 3:15. At 3:00 I found one and one-half dilation with arm in vagina. I dilated manually, but pains becoming less, I gave pituitrin at 3:50; pains became strong at 4:05 and increased to 4:30. I found one-third dilation with body presenting. Pains were very strong and delivered without turning at 5 p. m., becoming a complete breech delivery, the child being doubled or flexed which certainly is very rare. Placenta delivered at 5:15.

The points of interest are labor in progress from November 22d to November 28th, considerable discharge, not much dilation, cord prolapsed, elbow presenting and no pains, but with pituitrin, pains were immediate, and two injections, no doubt, saved hours of waiting and perhaps turning. I had not read of use of pituitrin under these conditions.

I was called December 20th to attend Mrs. W., pregnant six months. I examined at 5 a. m.; had been but little pain, no discharge, but membrane bulging and prominent and slight dilation. At seven I ruptured membrane and waited two hours for pains. At nine I dilated manually and she had some very slight pains, breech presenting. At 10:50 I gave pituitrin and in three minutes pain followed; child delivered 11:15.

The points of interest are waiting long enough to know nature will not act, then getting such prompt action from pituitrin.

I was called December 25th, 2:30 a. m., to attend Mrs. L. Found full term pregnancy and very feeble patient. She had some pain at 10 p. m., 24th, but not much. At 2:30 I found three-fourth dilation, at 5:00 slightly

more dilation, very weak pains and at 10:50 having had but slight pains and one-third dilation, I gave injection of pituitrin and at eleven very hard pains came on, the child being born at 12:30. I am confident in this case there would have been a very tedious, protracted, exhausting labor and probably forceps delivery. I consider that we have in pituitrin a most valuable aid in our obstetric work and hope others may be as well pleased as I am.

I would say, in warning, we should have a dilated or dilatable os before using it as pains follow so quickly and surely that uterine rupture could easily occur.

CALOMEL.*

L. S. Oppenheimer, M. D.,
Tampa, Fla.

Calomel has a vast army of skeptical unrelenting enemies, as well as a legion of credulous enthusiasts.

Indeed many practitioners handle it with misgivings and trepidation.

This conservatism is really due to the obscurity of our knowledge concerning its limitations and accounts in a great measure for the divergence of opinion of medical men about its safety and its virtues.

One man gives one grain hesitatingly, the other fears to give less than three, still another daring doctor delights in 50-grain doses.

The belief that calomel is converted into the bichloride is no longer entertained. This conversion was said to be caused by hydrochloric acid, chloride of sodium, other alkaline chlorides and certain acidulous drinks.

All researches have indicated that it is not changed or acted upon until it reaches the alkaline fluids of the intestines.

There are many varying opinions as to what chemical changes actually take place there.

Rabuteau thinks it is decomposed into fine particles of metallic mercury. Schaefer claims that mercurous and mercuric oxides are formed. Others believe the fatty acids in the intestines dissolve it.

Meyer and Gottlieb, who have studied its action very thoroughly, state: "By contact with the tissue fluids calomel is transformed into soluble mercuric compounds, probably albuminates, which, without causing any local toxic action, are absorbed very gradually. In the mucous membranes of the mouth and intestine this action causes a stimulation of glandular secretions and inhibition and by its disinfecting action combats to a certain extent the harmful bacterial flora of the intestines."

It is unknown in what form mercury is absorbed and circulated in the blood. When it is injected hypodermically in an insoluble form, the leucocytes take it up and carry it off as they do any other foreign insoluble body, and it is quite possible that they may take it up in the same way from the alimentary canal.

The most immediate action of calomel is on the intestines, where it has an irritant and stimulating action on the epithelium and the intestinal glandular secretions. When absorbed in sufficient quantities, it also has a stimulating action on the secretion of the salivary glands and on the kidney.

While it is popularly supposed that calomel stitmulates the secretion of bile, there is no experimental evidence to show that it acts directly on the liver at all, but the possibility of such an action is not absolutely denied. Meyer and Gottlieb state: "That the bile becomes more concentrated as a result of the dehydration which results from catharsis with calomel." This would indicate that it would have some direct influence upon the liver itself.

It is probable that calomel has some action as an intestinal disinfectant. Schamberg's investigations (1914) showed that calomel has a high germicidal power. In his

*Read before the forty-third annual meeting of the Florida Medical Association at Arcadia May 10-12, 1916.

experiments he found that 1-1200 grain (0.05 mg.) of calomel was sufficient to sterilize 0.1 c.c. of staphylococcus aureus, B. typhosus or B. coli in 10 c.c. of bouillon. His experiments, however, did not extend to its action in the intestines.

According to Schamberg, the action of calomel on the kidneys is supposed to be a direct stimulation of the renal cells, primarily of the tubules. With non-toxic and mildly toxic amounts apparently only the tubules are affected, with larger amounts changes are also found in the glomerules.

The toxicity of calomel depends upon the amount of mercury absorbed, not upon the amount of calomel taken into the system. The rate of absorption is slow (Schamberg found the rate to be only 1.4 per cent per day), and consequently if the calomel is removed quickly from the intestines very little is absorbed.

There are probably certain drugs, foods, personal idiosyncrasy, etc., affecting the chemical conditions in the intestines that would influence the rate of absorption for calomel, but as noted above, the chemical changes involved are as yet so little understood that the means of influencing them cannot be determined with any certainty.

If it is true that the alkalinity of the intestinal fluid is favorable to the decomposition and absorption of calomel, alkaline menstrua should hasten the process; Schaefer and Patein support this view, and the writer's observations bear this out.

In one case, some years ago, where two 10-grain doses of calomel and soda had been administered 6 hours apart, chloride of ammonium in 10-grain doses given every three hours, next day was promptly followed by very severe salivation. Since that time ample opportunity has been given to verify the power of the various alkaline salts given in conjunction with calomel.

Salivation is invited by constipation, slow elimination, small and medium doses, bowel paresis, co-administration of the iodides.

Purgative doses should be given if the bowels are not active, accompanied or followed by a cathartic, unless for special reasons the latter is to be withheld.

Large doses are not to be given with an alkaline salt, small ones may always be.

The small quantities of sodium bicarbonate usually accompanying calomel are neutralized by the stomach juices, except when taken while the gastric glands are inactive. To be effective more soda is required.

Small, repeated doses of calomel allay the nausea and vomiting of children.

Doses of 100 grains followed by a brisk cathartic is a very common practice by many physicians. The writer has observed several remarkable and prompt results in dissipating a general dropsy with these protean doses.

The indications for their administration are thus expressed in a letter from a progressive up-to-date Jacksonville colleague:

"I have given 100-grain doses of calomel dozens of times. Have given it to the same patients repeatedly at intervals of a few weeks or months. I give these doses in cases of anasarca, regardless of the cause, and have never known it to salivate or cause an undue amount of depression. Salt is excluded from diet on days of treatment. It has almost invariably relieved the effusion more completely and quicker than any other treatment of which I know.

"In one case of pronounced syphilitic heart lesion 150 grains were given on two occasions, with the happiest results. As a hydragogue cathartic in above cases it has no equal."

In the common bowel disturbances of infants some practitioners prefer the small repeated doses, others strongly advocate large ones. In bacillary dysentery castor oil is more reliable. All stools should be tested with blue litmus and acidity corrected.

In conclusion, the writer begs to admit that he lays no claim to having introduced

material, new personal evidence about calomel, but has been prompted to present this paper in the hope of clearing up some obscurities in the minds of many regarding its usage.

PROPAGANDA FOR REFORM.

WHY GLYCEROPHOSPHATES? — The glycerophosphates are split up in the intestines into ordinary phosphates and absorbed and utilized, if they are utilized at all. There is no evidence that glycerophosphates have any pharmacologic action to warrant the belief that they are of use as therapeutic agents. The belief in their value is kept alive by the promotion of certain proprietary mixtures. The glycerophosphates will be continued to be manufactured until physicians refuse to prescribe them. A manufacturer has even substituted glycerophosphates for the potent yellow phosphorus in his elixir of phosphorus, nux vomica and damiana and, so his chemist reports, physicians continue to prescribe the proprietary the composition of which has been altered. (*Jour. A. M. A.*, April 15, 1916, p. 1205.)

EMETIN HYDROCHLORID VARIABLE. — It should not be taken for granted that because a drug bears the name of a definite compound it is true to name and pure, and therefore trustworthy in its action. This fact has recently been demonstrated in regard to emetin hydrochlorid. Two cases in which the administration of emetin hydrochlorid produced symptoms of poisoning (one terminating fatally) at the Johns Hopkins Medical Clinic led to an investigation by R. L. Levy and L. G. Rowntree, in which the emetin hydrochlorid preparations of five pharmaceutical houses were used. This investigation led to the conclusion that the products supplied as emetin hydrochlorid are variable in composition and in toxicity to a degree which constitutes a serious danger. It behooves physicians to insist on some declaration from the firm supplying emetin hydrochlorid as to its purity and as to the standard employed. Levy and Rowntree emphasize also the fact that emetin hydrochlorid medication itself is not an innocuous procedure. To avoid the toxic effects of emetin, the dosage should be carefully adjusted for each individual and the treatment should be given in courses at intervals of several days or a week. The subcutaneous method of administration is to be preferred. (*The Archives of Internal Medicine*, March 15, 1916, p. 420.)

CACTUS COMPOUND PILLS—A pharmaceutical firm makes Pills Cactus Compound (Heart Tonic), each of which is said to contain: "Cactus grandiflorus ½ grain, Sparteine sulphate 1-40 grain, Digitalin, pure (German) 1-125 grain, Strychnine sulphate 1-500 grain, Glonoin (nitroglycerin) 1-500 grain, Strophanthin 1-5000 grain" The combination is irrational and the dosage of the individual drugs, in most instances, absurdly small. Every one of the ingredients except digitalin may be disregarded either because of inertness or because of the small amount present, and the treatment then becomes one of digitalis. The selling name of "Cactus Compound" is a misnomer as the activity of the pill is that of the small dose of the digitalis glucoside. The pill is an illustration of how worthless drugs are perpetuated. At one time it was thought that cactus had therapeutic value. During that time many "specialties" and proprietaries bearing its name were put on the market. Although the drug is now known to be worthless, these specialties continue to be sold. (*Jour. A. M. A.*, April 29, 1916, p. 1387.)

GENOFORM.—Genoform, advertised as a remedy for rheumatism, gout, neuralgia, etc., is marketed with the claim that it is split up in the intestines into salicylic acid, acetic acid and formaldehyd. The statement of composition is too indefinite to permit any real insight into its possible reactions, but even if formaldehyd is liberated in the intestines, Genoform could not have the properties which are claimed for it. (*Jour. A. M. A.*, Feb. 26, 1916, p. 676.)

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THE VOLUSIA COUNTY MEDICAL SOCIETY.

One of the most wide-awake units in the State Association is the Volusia County organization.

THE JOURNAL is pleased to call attention to one of their activities which might well be patterned after by other organizations throughout the State. A series of articles on matters pertaining to public health has been prepared by the Society to be published in their local papers under the auspices of the organization. The following article on "Feather Pillows," comprising one of the series, is timely and of general interest.

"Feather pillows are quite a departure from conditions which must have surrounded the primitive man. Surely the adoption of the feather pillow must have been an event suggesting luxury and free indulgence in expensive rarities at one time! Now they are considered a necessity. We take them as a matter of course. We have big fat ones and small limp ones. Their weight depends largely upon the quality of feathers inside. Have you ever stopped to think what the condition must be of the unseen confusion within a pillow tick? Have you ever stopped to think how much carbon dioxide from a thousand mouths may have been diffused into a pillow? Have you ever wondered how frequently pillows are renovated as they should be and how well it is done when it is supposed to be done at all? Have you ever noticed how musty and oily they may smell in hot weather? Have you ever thought of how they increase one's temperature in hot weather? Have you ever contemplated on how many generations may have used those feathers before you?

"Do feather pillows seem really sanitary when we reflect upon all this and in addition permit ourselves to remember how often they are used in illness and simply shaken up and put in a case and forgotten? Large pillows of any kind are objectionable because

of round shoulders they produce. Large pillows allow just that much more sinking of the head into the center and contribute to moisture about the head and ears which in turning the head invites congestion if one is in a draught or in a cool room. This moisture is unnecessary and invites catarrh of the head and ears. Persons with ear defects should remember this and avoid feather pillows. Babies should never have pillows except as fancy things to adorn a crib and adults will do well to discard anything but small feather pillows and what is better adopt hair pillows. Hair pillows are much more sanitary and after one gets used to them better in every way.

"No doubt the primitive man slept with a stone for a pillow. Civilized man is climbing far from nature in many ways and consequently invites complications. Hair pillows are plenty soft and certainly much more sanitary and do not cause the head and neck to perspire. They have no stuffy odor and can be easily sunned and aired because they are not so compact and need not be large. We can continue to use clean feathers for the opulence so necessary (as a result of custom) on a well-made bed, but we should adopt hair pillows for actual use, health and reason. Hair costs more, but a small hair pillow very little more than the average feather pillow in use. In this climate we have more reason to adopt the hair pillow than perhaps in colder countries. Fresh individual pillows should be the rule in cold climates if feathers are used, and in the South fresh individual hair pillows would be a wise departure for particular persons."

THE JOURNAL takes this occasion to congratulate the Volusia County Medical Society upon the good work they are conducting.

THE SACRIFICE OF THE CHILD TO CARELESSNESS.

As winter arrives with unprotected open fires, hot stoves and burning brush heaps, there occurs a marked rise in the number of deaths from accidental burns. It is conservative to say that ninety per cent of these deaths are the results of carelessness of adults, and most of the victims are helpless infants and children. In Chicago during the past fortnight two deaths occurred as a result of an older child setting fire to a younger one with a lighted candle; three deaths and one serious burning resulted when a child pulled over a pot of boiling water, coffee and potatoes, respectively; two serious burnings and one death followed "playing with matches." When death does not occur, the result is usually an extensive burn with horrible scarring and mutilation. It is pitiable to read that one mother left a 5-year-old child to "watch" a baby of 18 months, and in the room was a lighted candle. Carelessness and ignorance—their toll of deaths is greater than that of war.—*Journal of the American Medical Association.*

INTRAVENOUS THERAPY.

The intravenous administration of drugs is a new departure in therapy, but one which is rapidly increasing in use. Among its reputed advantages are that it is the quickest means of obtaining the effects of a drug, the effects are obtained with a certainty not obtained by other methods, and they are so marked that they cannot fail to impress the observer. These advantages in many cases are apparent rather than real; but even were they real advantages, they should not blind us to the various and serious dangers which this method involves. The technic, although not difficult, must be thoroughly mastered, or undue pain, infection, air embolism, or even death may result. Such accidents, however, are ordinarily easily avoided, and should be considered quite inexcusable. More serious is the fact that the drugs given intravenously reach the system, and especially the heart in a different manner and concentration from that to which physicians are accustomed with ordinary methods of administration. Pharmacologists have long

practiced intravenous administration, when studying acute effects of drugs, and they have observed that frequently the immediate result of such injections is a prompt fall of blood pressure, not obtained when the same drugs are given by mouth or even hypodermically. This fall in blood pressure is commonly attributed to irritation of the endocardium. It is usually of short duration, but is certainly undesirable and sometimes may have serious results.

It has also been observed that several drugs, for instance, quinin and potassium, depress the cardiac muscle when given intravenously much more than when given in other ways. Furthermore, any substance which tends to precipitate proteins must be injected slowly and with extreme caution, or it will produce intravascular clotting and sudden death. Deaths have resulted not only from a lack of knowledge of the technic of intravenous therapy but also from a lack of knowledge of drugs which may be so administered. Sudden death has been reported following the injection of an iron preparation containing peptone, and also following intravenous injection of ether. Intravenous injections, while sometimes superior to the slower methods, are distinctly inferior when a continuous rather than a sudden action is desired. Drugs leave the blood system with great rapidity, and therefore their action on the circulation will cease promptly unless they are continuously supplied. It would be undesirable to inject intravenously such drugs as iodids, nitrites, iron or salicylates.

With these dangers and disadvantages in mind, it seems unwise to resort to promiscuous intravenous medication until the effects of this method have been studied in detail for the drugs employed, and unless there are distinct advantages to be secured. This is the case when an immediate action is necessary in emergencies, as in the use of strophanthin for cardiac collapse, quinin in pernicious malaria, etc., or if the drug would be destroyed in the stomach or tissues, as in the case of salvarsan, or where the drug is not adequately absorbed by any other channel, as in the case of epinephrin.

Intravenous therapy will be most securely advanced if its employment is restricted to such well defined fields. These fields can be satisfactorily determined only by a scientific pharmacologic study of the action of these drugs when so administered in animals, as well as in man, under conditions in which the results are carefully controlled. The intravenous method is an impressive one, approaching in preparation almost to that which goes with a surgical operation. The patient is usually interested and impressed by this new, and to him, mysterious method. There is a psychic element in his reaction to the injection which is not a factor in his reaction to the same drug when given by mouth. The intravenous injection of a complex mixture would appear to be particularly reprehensible. Little is known, as has been stated, of the results to be expected from intravenous therapy, even with simple substances. The use of complex mixtures will without doubt react against the proper use of the method.—*Journal of the American Medical Association.*

Cancer Department

"In the early treatment of cancer lies the hope of cure."

AMERICAN SOCIETY FOR THE CONTROL OF CANCER

EARLY DISCOVERY OF CANCER. YEARLY MEDICAL EXAMINATION URGED FOR PREVENTION OF DISEASE.

The American Society for the Control of Cancer is strongly seconding the efforts of the National Association for the Study and Prevention of Tuberculosis to have December 6th set apart as "National Medical Examination Day." Among other observ-

ances planned for the day Dr. Harvey R. Gaylord, of Buffalo, Director of the New York State Institute for the Study of Malignant Disease, will deliver an address on cancer at Minneapolis under the auspices of the "Health and Happiness Week" arranged by the Minnesota Public Health Association in cooperation with other social and civic organizations.

The time is undoubtedly coming when Americans will appreciate the great wisdom of the Chinese policy of paying the doctor to keep the patient well. The rapidly-growing movement in favor of an annual medical examination for every person, sick or well, promises much benefit in the reduction of the death rate from cancer as well as that from tuberculosis. In both these very prevalent diseases the hope of cure is very much greater if the ailment be recognized and treated in the earliest stages. Cancer is by no means a hopelessly fatal disease and an ever-increasing number of those afflicted are being saved through their intelligent recognition of the danger signals and their prompt recourse to competent treatment. Undoubtedly many more cases of this disease would be recognized in time for treatment in the early stages, when cure is a comparatively simple matter, if the people were in the habit of consulting their physicians once a year or even at shorter intervals, and having a general physical examination.

Cancer patients are often persons who have generally enjoyed good health, have never been seriously ill and who at the time of the onset of the disease were apparently in robust health. This disease is so insidious in its approach and so often without pain in the first stages that the patient often fails to pay serious attention to the signs of danger. Statistics independently gathered by many surgeons prove that the average cancer patient waits a year or more after observing some suspicious condition before seeking the treatment which is then often too late. This disastrous delay is the main, if not the sole, obstacle to the successful treatment of cancer at the present time.

"Early cancer," says Dr. Charles P. Childe, a prominent English surgeon who has written one of the best popular books on the control of this disease, "produces no feeling of ill health whatever. In other words, early cancer has no symptoms. The reasons which usually induce people to consult a doctor are the suffering of pain or the feeling of ill health. Early cancer produces neither. People are far more likely to go to a dentist with an aching tooth than to a doctor with commencing cancer; they are far more likely to consult a doctor with some trifling derangement of the liver than on account of cancer in its early stages. Owing to the insidiousness of its onset, the victims of cancer are often totally unconscious of the seriousness of the disease which has attacked them. Disaster following on delay through sheer ignorance on the part of the unfortunate sufferers that there was anything seriously the matter with them—these are the every-day experiences of cancer." All good physicians, however, are familiar with the warning signs of the approach of this dangerous disease and if given a chance to examine their patients once a year, especially after the age of thirty, they could undoubtedly save many of them from death before their time.

NATIONAL BOARD OF MEDICAL EXAMINERS.

The National Board of Medical Examiners held its first examination from October 16th to 21st in Washington, D. C.

There were thirty-two applicants from seventeen States, representing twenty-four medical schools, and of these sixteen were accepted as having the necessary preliminary and medical qualifications, ten of whom took the examination.

The following men passed:

Dr. Harry Sidney Newcomer, John Hopkins University.

Dr. William White Southard, John Hopkins University.

Dr. Orlow Chapin Snyder, University of Michigan.

Dr. Thomas Arthur Johnson, Rush Medical School.

Dr. Hjorleifur T. Kristjanson, Rush Medical School.

The second examination will be held in Washington, D. C., June, 1917. Further information may be had by applying to Dr. J. S. Rodman, Secretary, 2106 Walnut Street, Philadelphia, Penna.

THE VITAMINE CONTENT.

The interest of physicians the country over has been greatly aroused by the publication of Reprint No. 333 from the Public Health Reports. The article is entitled Bread as a Food, and Diseases, Malnutrition and the Vitamine Content in its Relation to Pellagra.

The conclusion of the article that a reduced vitamine content of the diet immediately preceded the rapid increase of pellagra in that section is important as showing the cause of the disease, but the influence of the careless and indiscriminate use of soda in cooking as a cause of the reduced vitamine content of the diet is almost equally important. It shows the necessity of the physician giving advice to the housewife in regard to her methods of cooking.

The use of soda in cooking leaves the food alkaline and the alkali destroys the vitamines. If, however, a proper amount of an acid ingredient is used the food is not alkaline and the vitamines are not destroyed. In cooking breadstuffs it has become a custom to use soda only as a leavening agent in certain sections of the country. In these sections pellagra has been prevalent. The physician must take note of this custom and advise its discontinuance.

In other sections milk or sour milk is used with the soda. This is a better practice, but still is fraught with grave danger. The amount of sourness, or lactic acid, must be guessed at and the corresponding amount of soda also guessed. The housewife seldom ever does any guessing because she does not understand that a relationship exists between the sourness and the soda. She adds what she considers enough soda to leaven and what she considers enough milk or sour milk to enrich and moisten. As a result the food is most often alkaline. The physician should advise against incurring these dangers. They can be absolutely avoided by the use of properly made baking powder using sweet milk if desired. All well-known brands of baking powder are manufactured under chemical supervision and are reliable, while the housewife's rule of thum methods with soda are dangerous in the preparation of breadstuffs.

Breadstuffs are the principal food material of a great class of the people and their vitamine content is therefore to be husbanded and not destroyed. If as a result of the economic depression beginning with the year 1907 the cost of food has increased out of proportion to the increase in wages, and that the pellagra incidence has also increased considerably since 1907, what are we to expect with the war prices that prevail today, which are felt all over the country. From 1907 there took place a reduction in the diet of the people of such foods as milk, eggs and meat, with a consequent reduction in the vitamine content of the diet. A like reduction is taking place on an even larger scale today and therefore there is the greater need of husbanding the nutritious qualities of bread and cereal products in general.

In this connection should be considered self-raising flour. This is a product containing soda, salt and an acid ingredient. If properly compounded the soda and acid should neutralize each other and no alkali left in the food to destroy the vitamines. Self-rising flour, however, is being manufactured largely by housewife rule of thumb methods, without chemical supervision. It contains phosphate rich in calcium sulphate

which latter is undesirable in food products. The use of a standard baking powder and a good flour is cheaper for the consumer and is safe. The latter consideration should overcome the tendencies to laziness to which weakness, only, self-rising flour caters.

COMBATING INSECTS AFFECTING THE HEALTH OF MAN.

Activities of the Bureau of Entomology of the United States Department of Agriculture Shown in Annual Report.

Continued advances in the work of combating the activities of insects affecting the health of man are reported by the Chief of the Bureau of Entomology of the United States Department of Agriculture in his annual report recently issued. In mosquito investigations in Louisiana a species of mosquito hitherto considered a non-carrier of malarial infection was proved to be a carrier. Studies have been made of malaria and measures are being evolved to meet plantation conditions.

The "starvation" plan, aimed to exterminate the spotted fever tick of the Bitter Root Valley, Montana, was followed during the year with encouraging success. The plan consists of the removal of the domestic hosts of the adult tick from the infested areas. The Bureau also conducted a campaign of extermination against ground squirrels and other rodent hosts of the immature ticks. Examination of the rodents killed showed 40 per cent lower infestation by the tick than during the preceding year.

The report directs attention to the demonstrations of the Bureau specialists that the breeding of flies in manure can be prevented by treating the substance with calcium cyanamid and acid phosphate, which at the same time increase the fertilizing value of the manure.

The Bureau also conducted investigations into methods of lessening fly infestation in packing establishments operated under the Meat Inspection Service of the Department.

THE SOUTHERN GASTRO-ENTEROLOGICAL ASSOCIATION.

The Southern Gastro-Enterological Association was organized in Atlanta on November 15th while the Southern Medical Association was in session there.

Active membership in this society will be limited to those investigators and practitioners of the seventeen southern states who confine their work exclusively to diseases of the digestive tract.

It will be the policy of the association to hold its regular meetings annually, the next place of meeting yet to be announced.

The following officers were elected: Dr. J. C. Johnson, Atlanta, president; Dr. J. T. Rogers, Savannah, vice-president; Dr. Marvin H. Smith, Jacksonville, secretary-treasurer.

Councillors: Dr. S. K. Simon, New Orleans; Dr. G. M. Niles, Atlanta, and Dr. Seale Harris, Birmingham.

Admission and Ethics: Dr. George C. Mizell, Atlanta; Dr. J. E. Knighton, Shreveport; Dr. J. B. Fitts, Atlanta.

NEW AND NONOFFICIAL REMEDIES.

SOLUTION OF HYPOPHYSIS—SQUIBB. — A sterilized, aqueous solution of the water-soluble active principles of the posterior lobe of the pituitary bodies of cattle, free from chemical preservatives and physiologically standardized. It has the properties of the pituitary gland, as described in New and Nonofficial Remedies, 1916. E. R. Squibb and Sons, New York. (*Jour. A. M. A.*, Sept. 2, 1916, p. 745).

LIQUID PETROLATUM — SQUIBB, HEAVY (CALIFORNIAN).—It is made from Californian petroleum and is claimed to be composed chiefly of hydrocarbons of the naphthene series. A brand of liquid petrolatum complying with the U. S. P. standards for liquid petrolatum and claimed to be superior to liquid petrolatum, U. S. P. E. R. Squibb and Sons, New York. (*Jour. A. M. A.*, Sept. 23, 1916, p. 953.)

Publisher's Notes

HALF A CENTURY'S PROGRESS

October, 1916, points an epoch in the history of Parke, Davis & Co. The house was founded in 1866—just fifty years ago this month—largely upon the optimism of three or four determined men, backed by a capital that would seem insignificant today. There was nothing in its unpretentious origin to foretell the success of after-years. And by success we mean not merely material prosperity, but also that broader and more enduring success that is based upon good-will and confidence.

Manufacturing pharmacy was then a crude, imperfect art. Bacteriology, pharmacology and biological pharmacy were as yet unborn. There were no curative sera or vaccines in those days. Prophylaxis was in its infancy. Standardization was unknown.

Fifty years have wrought marvelous changes in means and methods for the treatment of human ills. The materia medica has been amplified beyond the dreams of the earlier investigators. Knowledge of pathology has immensely broadened. The empiricism of the past has given way to rational therapeutics, and medicine is taking its rightful place among the sciences.

In all these forward movements Parke, Davis & Co. have had some part—notably as discoverers of new vegetable drugs, as inventors of new chemical compounds, as pathfinders and producers in the field of biological manufacture, as investigators in original research, as pioneers in both chemical and physiological standardization.

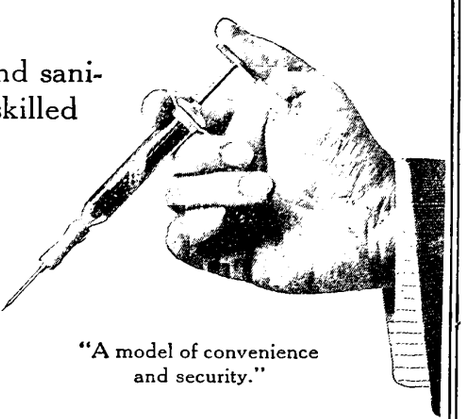
The past half-century, as we have intimated, has been remarkable in its contributions to the newer materia medica. What will the next fifty years bring forward? Time alone can write the answer. Ours is a progressive age. The science of medicine has not reached its highest development. The physician's armamentarium will be further enlarged and fortified. New remedial agents will come into being. Many existing products will be improved. And with the fulfillment of these conditions, Parke, Davis & Co. (if we may judge the future by the past) are certain to be identified.

The specification "Parke, Davis & Co." on your orders for diphtheria antitoxin will insure a pure and potent product.

In the manufacture of our diphtheria antitoxin scientific methods mark every step of the process.

1. We conduct a biologic farm of more than six hundred acres—a home of natural environment for the animals used in the production of our antitoxin.

2. Our biologic stables are modern and sanitary. They are under the supervision of skilled veterinary surgeons.



"A model of convenience and security."

3. The health of our serum-producing horses is most carefully maintained. No animal is eligible for service that has not been pronounced sound and healthy by expert veterinarians.

4. Immunization and bleeding of horses are conducted in accordance with modern surgical methods.

5. The antitoxin is developed with scrupulous care, every method and appliance being in strict conformity with scientific procedure.

CONCENTRATED

Antidiphtheric Serum

(GLOBULIN)

is tested and retested, bacteriologically and physiologically. It goes to the physician with a positive guaranty of purity and activity.

Bio. 16—1000 antitoxic units. Bio. 20— 5000 antitoxic units.
Bio. 18—3000 antitoxic units. Bio. 22—10,000 antitoxic units.
Bio. 23—20,000 antitoxic units—supplied on special order.

SEE THAT YOUR DRUGGIST IS ABLE TO SUPPLY YOU.

Home Offices and Laboratories,
Detroit, Michigan.

Parke, Davis & Co.