fused with normal blood, he will make a prompt recovery, and be around again in a day or two. Clinicians tell us that pernicious anemia is usually a fatal disease, no matter what we do for it. There are the ups and downs, the periods of betterment alternating with periods of depression. We have not yet determined the hemolytic factor that causes the destruction of the red cells in pernicious anemia. It has been our experience in filling these people with new blood that they lose it in eight days, and return to the condition they were in before the transfusion. It was simply a temporary measure tiding them over for a few days. The method should not be followed out generally, because its use may result in useless operation without effecting the ultimate cure of the patient.

As to transfusion in tuberculous patients: The serum from tuberculous patients hemolyzes the normal red cells. In transfusing a tuberculous patient we run a great danger from active hemolysis occurring at the time of transfusion, with the resulting death of the patient, so that in doing transfusion in the case of a patient with active tuberculosis we must be careful that no hemolysis takes place. Clinically, this is shown by ascites in pericardium, pain and cyanosis, without dilatation of the heart. In a case of tuberculosis in which Dr. Crile transfused with normal blood, the patient seemed to do better than did those who did not have the transfusion, but you must shut off the transfusion when the patient begins to complain of pericardial distress with rapidity of the pulse rate.

DR. B. M. BERNHEIM, Baltimore, Md.: In regard to transfusing in pernicious anemia, we talked with Dr. Sloan yesterday and he said that he did not think it was advisable to do it. I asked him whether he had ever transfused a case early in the course of the disease, and he said no. If you will look up the literature, you will find that no one has transfused a case early in the course of the disease. The patients transfused have been nearly moribund. They were treated by physicians and as a last resort were brought in for transfusion, and it was done as an almost hopeless effort to save the patient. I do not believe that it helps matters much to reason about this matter, and to say that we do not know the cause of the blood destruction. That is true. It seems to me that we might take the case immediately after the diagnosis is made, while the patient has some fight left in him, and while his hemoglobin is still up to fifty or sixty per cent. Instead of giving him arsenic and the usual treatment, which is always fatal, why not try a few cases which might give a different result? As regards instruments for transfusion, Dr. Kimpton's instrument seems to be a good one, but no man can use that tube unless he has worked in the laboratory and has paraffined a tube not only once, but many times. No one else can do it. No one can do transfusions in general unless he has tried beforehand. If a man has worked up his technic on animals and developed it, he can do a successful transfusion by any method. The two things are parallel.

DR. V. C. VAUGHAN, JR., Detroit, Mich.: Some ten months ago I had a case that needed immediate transfusion. The patient was difficult to operate on—a new-born babe. We proved that we could withdraw blood from the donor and by the proper use of saline solution mixed with blood inject it from a hypodermic syringe into the vein of the recipient before it clotted. Dr. Freund of Detroit devised the apparatus. We have two needles, two rubber tubes, going to two-way stop-cock. To this stop-cock is attached a glass tube, with a container for normal saline. One needle is thrust into the vein of the donor, the other into the vein of the recipient. We fill the syringe with 1 c.c. of saline solution. Then the stop-cock from the vein of the donor is opened, and we fill the syringe with blood. Then this cock is shut off and the other is opened, and we force blood into the vein of the recipient. That requires no operation, you do not have to cut the skin. We have transfused 150 c.c. without detaching the needles. Anyone can use the method. The blood does not clot.

THE BROMID QUESTION EXPERIMENTALLY CONSIDERED

I. THE RESPONSES OF THE HEART TO BROMID PERFUSION *

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Potassium bromid was first prepared by Ballard in 1828. The bromid salts were soon found to be depressant to nerve reactions, for which purpose they have been in use in therapeutics for many decades. In 1868 Rabuteau¹ demonstrated bromid retention in the animal organism after continued bromid feeding. This was of peculiar interest because of the well-known fact that other members of the halogen group, namely, the iodids and chlorids, are rapidly eliminated.

The literature of the bromids is voluminous, but little of it directly concerns the pharmacologic reactions in the body. In 1877 Krosz² gave a thorough review of the older literature (to 1875). Busquet and Pachon³ in 1909, studied the relative toxicity of the bromids as compared with other potassium salts in relation to the activities of the rabbit's heart. Aside from these papers the most valuable contributions to the literature are those that have been determined secondarily in other physiologic studies, including the field of comparative literature on the salt action.

In our laboratories we have undertaken the pharmacologic reexamination of the bromids. It seemed to us advisable to first lay the foundations of our work in a careful examination of the reactions of the organs other than the nervous system to the bromids. In the present paper, therefore, we wish only to report a phase of the work; namely, the reactions of the heart and cardiac apparatus to bromid nutrient mediums.

THE BROMIDS ON THE HEART

The experiments here reported were performed on the hearts of frogs, and on the isolated heart of the warm-blooded animals. As a result of the last four decades of physiologic experimentation it is now well known that not only the heart of the cold-blooded animal but also that of the mammal as well responds very normally in both rhythm and amplitude of contractions through many consecutive hours when fed on a physiologically balanced oxygenated saline solution. Especially through the work of Howell and his pupils we have assumed that the cations or bases are the all-important factors in these inorganic salt solutions, and have given relatively little attention to the anions. Of course, it is taken for granted that isotonicity is a very necessary, in fact absolutely essential, factor under all circumstances. Loeb in numerous papers has emphasized the physical constants, especially that of permeability.

The experiments in this field, for the most part, rest on the assumption that the chlorid anion is relatively indifferent toward the living tissue of the organs—of

* Read in the Section on Pharmacology and Therapeutics of the American Medical Association, at the Sixty-Fourth Annual Session, held at Minneapolis, June, 1913.

1. Rabuteau: Recherches sur l'émanation des bromures, *Gaz. heb. de méd.*, 1868, 37.

2. Krosz, I. G.: Ueber die physiologische Wirkung des Bromkallium, *Arch. f. exper. Path. u. Pharmacol.*, 1877, vi, 1.

3. Busquet, H., and Pachon, V.: Contribution à l'étude de la mesure quantitative des actions d'ions sur les organes vivants et isolés. *Jour. de Physiol.*, 1909, xi, 243.

the heart in particular. It has been assumed that the changes observed in the heart under variations in the saline content of its nutrient fluid are primarily dependent on the variations in the cations. Of these cations the all-important and best-investigated ones are sodium, potassium and calcium.

Starting from this point of view we have carefully examined the variations in reactions of the heart to neutral solutions in which the bromid salts have been substituted for the chlorid salts. In every case our stock solutions have been made up of isotonic concentrations, namely, one-eighth molecular solutions.

RESPONSES OF THE HEART TO BROMID SUBSTITUTIONS FOR THE CORRESPONDING CHLORID CONSTITUENT OF PHYSIOLOGIC SOLUTIONS

Physiologic solutions are based on maintaining the physical and chemical balance represented by the blood. Such solutions must first of all be isotonic with the blood-plasma, a factor which is all-important in every artificial solution. The most commonly used solutions are of course physiologic saline, and Ringer's solution or its modifications. Ringer's solution represents a balanced saline consisting of sodium, potassium and calcium chlorids in proportions present in the normal blood. We have tested the bromids, first, by making a sodium bromid isotonic with physiologic saline; second, by substitution of the corresponding bromid salts in equimolecular quantities for the chlorids in Ringer's solution. These substitutions have been for individual chlorids and for the various possible groups in the solution. The final test has been in entirely displacing the chlorids with what may be called a bromid Ringer's solution.

SODIUM BROMID SUBSTITUTED FOR SODIUM CHLORID IN PHYSIOLOGIC SALINE

Considering the first line of experiments; namely, the sodium bromid for a physiologic saline, we report that so far as the cold-blooded heart is concerned it is exceedingly difficult to demonstrate any sharp physiologic change in reaction of the heart to this solution. It is well known that sodium chlorid alone will not sustain cardiac contractions and that the heart responds to it (NaCl) alone with a characteristic cycle of changes in rate and amplitude. Bromid saline gives almost the identical cycle of changes.

There is a slight variation in the response, but so slight that it would scarcely deserve mention but for the fact that it is quite constant; namely, a tendency to a slightly greater rate in the initial stage of the bromid perfusion, with a somewhat greater depression in the later stages. In other words, the so-called toxic influence, if one apply that term to physiologic saline, is a trifle greater with bromid perfusion.

THE INFLUENCE OF A BROMID-RINGER'S SOLUTION ON THE HEART

Omitting for the present consideration of partial substitutions in the Ringer's solution, attention may be called to the reactions of the heart to a pure bromid-Ringer's solution. The bromid solution used consisted of sodium, potassium and calcium bromids in equal molecular concentration with the corresponding chlorid in the normal Ringer's as we use it in the laboratory. This would give, stated in percentages, the following solution:

BROMID-RINGER'S		
Sodium bromid	1.29	per cent.
Potassium bromid	.048	per cent.
Calcium bromid	.042	per cent.

This is isotonic with the following normal Ringer's solution:

Sodium chlorid	.73	per cent.
Potassium chlorid	.03	per cent.
Calcium chlorid	.026	per cent.

Frog hearts were perfused with the foregoing bromid-Ringer's solution alternating with chlorid-Ringer's, and also with continuous bromid-Ringer's perfusion through many consecutive hours.

It is well known that the frog heart will remain alive and rhythmic for several days when perfused with normal Ringer's solution, provided only that bacterial infection shall be eliminated. In our laboratories the bromid-Ringer's sustained the heart through twenty-eight hours' consecutive perfusion, the organ still giving good strong contractions at the end of that period. In this instance no effort was made to keep the preparation sterile.

The factor that seems to be relatively constant, though at the same time it must be considered as quantitatively slight, is a mildly accelerated rate, especially in the early stages of bromid perfusion. In the late stages there usually follows a relatively greater decrease in rate under the bromids. These differences are slight and possibly should not be strongly emphasized. At the moment of change from one solution to the other, when it can be assumed that there is an admixture of chlorids and bromids passing through the heart, there is usually a rather pronounced acceleration which affects both amplitude and rate. This can be assumed to be the period when there is a dissociation of ion-protein compounds in the tissues with a shift from the chlorid to the bromid compounds, a factor that probably accounts for the relative instability of the protoplasm at this particular period.

PARTIAL SUBSTITUTIONS OF THE BROMIDS IN A RINGER'S SOLUTION

The experiments in which only one or two of the chlorid salts were replaced by bromid salts practically coincide with the observations which have just been presented. If one gives careful attention to exact isotonic equivalents and maintains a physiologic balance of the cations in solution, then it is practically an indifferent point as to whether the anions shall be chlorid or bromid in so far as the physiology of the cold-blooded heart is concerned.

Experiment to Show the Influence of a Bromid-Ringer Solution Substituted for Chlorid Ringer on the Isolated Heart of a Young Cat.—The heart was kept beating by coronary perfusion with Ringer's solution three parts, and cat's blood one part. At a point the solution was displaced by isotonic bromid solution three parts, and cat's blood one part. The normal rate just before the change was 150 per minute, the amplitude 17 mm. During the perfusion and after one minute the rate was 150, the amplitude 13 mm. After one and one-half minutes the rate had dropped to 141, the amplitude to 11 mm. When the normal Ringer was returned it took a few seconds to displace the bromid Ringer but in ten seconds after the shift the rate was 132, the amplitude 10 mm., showing the greatest bromid depression. One minute later the rate was 135, the amplitude 12 mm. From this time the amplitude and the rate slowly recovered to approximately the normal.

An incomplete series of tests has been made on the relation between the vagus nerve and the frog heart under bromid perfusion. It is well known that under perfusion with Ringer's solution, the vagus nerve maintains its controlling relation to the heart muscle with little change in its efficiency. The vagus nerve is still

active under bromid perfusion, but our series of experiments is not complete enough to state whether or not there is local change in sensitiveness to vagus control.

EXPERIMENTS ON THE ISOLATED MAMMALIAN HEART

From the therapeutic point of view, reactions of the warm-blooded heart to the bromids is of more interest perhaps than the reactions of the cold-blooded heart. We have made a number of tests by a method which depends on coronary perfusion. Isolated cat hearts were maintained under a perfusion of 3 parts chlorid-Ringer's solution, and 1 part cat blood. A carefully balanced bromid-Ringer's diluted with the same amount of cat blood was used for testing the bromids.

The warm-blooded heart is more sensitive to the bromids than is the cold-blooded heart. Our tests have not been absolutely constant. Out of thirteen experiments three showed primary acceleration of rate, which is generally obtained in the cold-blooded heart. The remaining experiments show primary depression in rate. In all experiments there was a depression of amplitude. If the bromid perfusion was for only a relatively short period then there followed a gradual but slow recovery in both rate and amplitude on renewing the normal Ringer's and blood. In long bromid perfusions arrhythmia often sets in which may be removed with chlorid-Ringer's blood.

DISCUSSION OF RESULTS

In summarizing these results one must admit that the inorganic bromids are relatively indifferent to such organs as the heart of the cold-blooded vertebrates. On the hearts of warm-blooded animals the bromids are in the long run sharply depressant whether they be measured by rate or by amplitude. If the bromids are combined with bases in strictly physiologically balanced solutions they are relatively non-toxic, especially to cardiac muscle. On the other hand, if the salts are used without reference to the physiologic balance of bases it often happens that reactions of the heart are relatively misleading, owing not to the primary toxicity of the bromid anion but to the influence of the base or cation. This is particularly true of potassium bromid. Looking over the literature we cannot escape the conclusion that many of the so-called bromid therapeutic effects are distinctly chargeable to the base with which the bromid has been combined.

Correlation between Complexion and Resistance to Auto-Intoxication.—I should like to call attention to the extraordinary variation in the resisting power of the individual as manifested by the color of the hair, not only to the changes in the fat and color of the skin already referred to, but to all other consequences of auto-intoxication. The darker the hair the lower is the resisting power to auto-intoxication, and the more conspicuous are the changes which result from it. On the other hand, if the hair is red or of a peculiar towy color the individual has a minimum of resisting power to the action of these poisons, and that resisting power varies directly with the distribution and with the intensity of the redness of the hair. This is manifested very conspicuously in the influence exerted by the toxins on the appetites of the individual. The darker-haired subject will loathe the sight of food and frequently abhor any sexual relationship, while the red-haired subject rarely manifests these effects, even in the extreme conditions of intestinal stasis. This influence of toxins on the normal appetite is of far-reaching importance in our present state of civilization and is the source of much misery, discontent and trouble, to which I will not do more than allude here.—F. W. Andrewes, M.D., in *Proc. of the Royal Soc. of Med.*

NON-SURGICAL TREATMENT OF CIRRHOSIS OF THE LIVER *

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In discussions of portal cirrhosis of the liver (atrophic cirrhosis) it is stated that death with rare exceptions occurs in from six to eighteen months after the appearance of ascites and other symptoms most characteristic of the disease. For years I watched cases of this disease running a course of the duration mentioned, and alleviated the discomfort of the patients as best I could; but I treated them without hopefulness.

After patients with this disease began to be treated surgically I saw a few recover and return to work; but more of them promptly ran a fatal course. For example, recently I saw a stout and vigorous policeman who had a Talma operation ten years ago on my recommendation.

Moreover, a case of spontaneous recovery came under my observation. A man aged from 55 to 60, with ascites, some anasarca, a quick, weak heart, and cirrhotic liver was under my care in Wesley Hospital. Traces of albumin and casts were found in the urine at first from time to time, but after a few weeks they were constantly present in small quantities. The radial arteries were thickened. He was placed on a milk and farinaceous diet, kept in bed and given physie. To the surprise of those of us who were watching him, the anasarca lessened and disappeared. Later but much more slowly the ascites lessened and finally disappeared. Simultaneously the heart grew stronger. He left the hospital and returned to his work as a shoemaker. About eighteen months later he was brought back to the hospital with all of the symptoms of chronic interstitial nephritis and uremia. In a few days he died and came to necropsy, when general arteriosclerosis, hypertrophy of the heart, contracted kidneys and atrophic cirrhosis of the liver were demonstrated. The development or progress of the renal lesion and hypertrophy of the heart evidently caused the disappearance of dropsy originally due to the cirrhosis of the liver. Rest and suitable dietetic treatment helped to produce a physiologic recovery from the hepatic disease.

Such cases prompted me to study again the literature of hepatic cirrhosis, endeavoring to find some clue to a rational treatment of the disease.

It need not be said that the anatomic changes in the liver produced by this disease cannot be removed. The symptoms which precede fatal results, however, are symptoms of impaired function and intoxication and are not due to the extent of the anatomic changes. It has long been known that extensive advanced hepatic cirrhosis is often found at necropsy in those who never have had ascites or other of the later symptoms of the disease. On the other hand, a mild grade of cirrhosis is sometimes associated with ascites and the symptoms of fatal disease. To repeat; the grade of cirrhosis is not the factor which leads to fatal results.

Pathologists have taught us another lesson. They find that a history of ascites and of other symptoms of hepatic insufficiency characteristic of the disease are wanting in 50 per cent. or a little more of the cases seen at necropsy.

Therefore we are justified in concluding that life and apparent health are compatible with extensive hepatic

* Read in the Section on Pharmacology and Therapeutics of the American Medical Association, at the Sixty-Fourth Annual Session, held at Minneapolis, June, 1913.