sities, which we all feel as such, can be converted into far-reaching sharply formulated equations, as was done by Carnot and Clausius. These principles were first applied in chemistry by Horstmann. Then, by successive application to chemical problems by Massieu, Gibbs, Helmholtz and others, was won a system of relations touching the problem of affinity, to which I can give only brief attention:

1. Affinity may be defined as the maximum quantity of work that a chemical change can produce. Equilibrium ensues when this quantity is zero.

2. The mass law can be obtained in a well-founded and somewhat modified form, restricted to dilute gases and solutions.

3. The Thomsen-Berthelot principle assumes a modified form in the rule that a fall of temperature induces the formation of that which develops heat. It is, for instance, in accordance with this rule that at ordinary temperatures water is stable in comparison with detonating gas, and that at high temperatures this relation is reversed, as it was found by Deville to be.

4. Lastly, we have the phase rule, indicating, for example, in what cases chemical phenomena will be comparable with melting and freezing, and in what cases they will be comparable with evaporation and condensation.

Most curious of all, we can treat problems of affinity in an absolutely trustworthy way, so that our calculations furnish a check upon experiment, without admitting anything concerning the nature of affinity or of the matter wherein the affinity is supposed to reside.

J. H. VAN'T HOFF.

THE PROBLEM OF RENAL FUNCTION.[1]

IN my first lecture I touched upon a series of physiological problems that have been elucidated in a pharmacological way. I treated these problems in a merely cursory manner and did not enter upon details of the various investigations. Permit me to-day to discuss more fully a problem which has for a long time claimed my attention and which has for many years been a topic of research in my laboratory, namely, the problem of renal function.

As is well known, there are two leading and opposing theories on the nature of urinary secretion. According to one of these theories, which was developed most fully by Heidenhain, we have to deal with a true secretory process by which water and perhaps the salts pass through the glomerulus, whereas the specific constituents of the urine are liberated from the tubules so that the sum of both secretions is represented by the outflowing urine. According to the other hypothesis, which was first proposed by Ludwig and subsequently modified (in a biological sense) by his successors, there goes on in the kidney, side by side with the glomerular activity, dependent essentially on the mechanical conditions of the circulation, and independently also on the secretion of certain urinary constituents, a process of resorption in the urinary tubules. Through this resorption the slightly concentrated secretion of the glomerulus, corresponding to the water of the blood, undergoes concentration to a point characteristic of the urine.

The output of urine is chiefly conditioned on the largely physical excretory process, which, on account of its dependence on the blood flow, and the blood pressure in the kidneys, one is justified in regarding as a kind of filtration or transudation. On the other hand, the resorption of water through the tubules is not directly dependent on the circulation of the blood. That is, it is in nowise proportional to the abundance of

[1] Being the second of the Herter Lectures delivered at the Johns Hopkins Medical School.

the glomerular filtration. It would be more nearly correct to say that this process is inversely proportional to the filtration. There is, therefore, the more abundant and unconcentrated urine when the blood flow is more abundant, and, on the contrary, a more scanty and concentrated urine when the blood flow is scanty.

The Ludwig theory, as you are aware, is based chiefly on the directly evident dependence of the urinary secretion on the blood stream through the kidneys and on the blood pressure, and in fact this connection is a striking one. I will remind you of the experiments of Goll, which were conducted as long ago as the year 1854, in which the tension in the vessels was lowered by vagus irritation or by bleeding, or elevated by clamping the large vessels of the extremities, in which the volume of the urine rose and fell according to the increased or diminished flow of blood through the kidneys.

Against the whole theory of Ludwig, supported as it was on many other facts and arguments, Heidenhain brought a series of objections, of which the following was especially impressive. If the human blood holds about one tenth of one per cent. of urea and if it be estimated that the daily excretion averages about 30 grams of urea, it would follow that on the smallest estimate 30 liters of fluid must filter through the kidneys in twenty-four hours, for which about 28 liters of water must be reabsorbed. But if, according to the calculation of Heidenhain, not more than 130 litres of blood pass through the kidneys in the course of a day, it follows that according to Ludwig's view about one quarter of this volume filters out—a condition which would lead to a wholly impossible concentration of the blood in the glomerulus. In addition to this objection was urged the uneconomical work involved in the resorption through the urinary tubules of such great quantities of superfluous water. But we now know through the careful investigations of Tigerstedt that there flows through the kidneys during a very moderate diuresis in one minute a quantity of blood corresponding to 80–100 per cent. of their weight, or, in other words, since the human kidneys weigh about 300 grams, these organs are traversed by about 240–300 grams of blood in a minute, equivalent to 345–430 liters in twenty-four hours. Thus it is only about one twelfth to one fourteenth of the volume of blood and not one fourth of its volume, that is expressed. And so far as the chemical work of resorption is concerned, it must be remembered that the work of excreting 30 grams of urea through the elective action of the tubular epithelium from blood holding only 0.1 per cent. of urea must be exactly as great as the corresponding work of resorption by the same cells—in order to concentrate a 0.1 per cent. blood filtrate to 1.5 per cent. of urea through the resorption of water. Now Heidenhain endeavored to demonstrate the specific secretory function of the epithelia by means of injection of coloring matters. He injected into the veins of a rabbit a definite quantity of sodium sulphindigotate and removed the kidneys after a certain period of time, injected the vessels with alcohol and examined the structures histologically. He then found under certain conditions that the glomeruli were wholly free from coloring matter; the epithelia of the tubules, on the other hand, were colored. And he concluded from this that the dye was not secreted from the glomerulus but was secreted by the tubules. And from these observations Heidenhain made the inference that the epithelia of the tubules secrete also other constituents of the urine. These experiments are so well known that

I do not need to enter more fully upon them; what concerns us here is that they secured a wide acceptance for the Heidenhain theory. But since the pharmacological study of glandular secretion as compared with renal activity has shown that these forms of cellular function are different and even opposed to one another in certain respects, and since the behavior of certain pharmacological agents is difficult to harmonize with the Heidenhain view and easier to bring into accord with the theory of Ludwig, a number of pharmacological studies have been undertaken with a view to testing the validity of the Ludwig theory. If, as Heidenhain maintained, the coloration of the kidney is an indication and measure of its normal secretory activity, it might be expected that by means of experimentally increased diuresis this coloration would show corresponding alterations, that is to say, coloration would be intensified in the tubules. With this idea in mind Sobieranski, about ten years ago, began a new study of this subject in my laboratory by means of color injections, carried out according to the Heidenhain method. His results on normal animals led him to the conclusion that dyes were not excreted by the convoluted tubules, as Heidenhain thought from his findings, but in company with the water stream through the glomeruli, whence the dye passed into the tubules and was absorbed into the epithelium, coloring their nuclei. Through the simultaneous reabsorption of water by the tubules, the dye-stuff solution becomes more and more concentrated so that it (the dye) under certain conditions is bound to be separated in a crystalline state in the epithelium.

This had already been shown to be the case by experiments with sodium sulphindigotate, but still more clearly by means of experiments with carmine, a dye which is better adapted to this kind of experimentation because it does not undergo reduction (with loss of color) in the tissues. Even more surprising and striking were the results obtained on diuresis under the influence of caffeine, sodium nitrate or urea. Here the tubules were found to be very little or not at all colored. It was thus shown that an increase in the secretion of the dye through the tubular epithelium, which the hypothesis of Heidenhain calls for, under these circumstances did not exist. On the other hand, the process becomes intelligible through the explanation of Sobieranski. These diuretics give rise to diuresis by inhibiting the absorption of water from the urinary tubules, and at the same time prevent the absorption of the coloring matter by the tubular structures. Against this interpretation of Sobieranski's findings it is possible to offer certain objections, the validity of which we have recognized from the beginning. The experiments of Sobieranski can be regarded as corroborative evidence of the resorption function of the urinary tubules, but not as positive proof of this function.

One may approach the subject, also, from an entirely different side. If the process of separating water from the blood in the glomeruli is not an elective secretory process, as in other glands, but is in reality a process analogous to filtration, that is to say, is essentially dependent on physicochemical conditions, then one would expect, as Tammann has already shown, that together with the free water of the blood (not held by the blood colloids) the dissolved crystalloid constituents, like urea and salts, would simultaneously filter through; in other words, that with increased separation of water these bodies would also be excreted in increased amounts. On the other hand, the colloids and other substances similarly held in the

blood, which can not transude or filter through the normal glomeruli are not driven through with the water flow. They must rather be secreted through specific cell activity and quite independently of all mechanical filtration.

Indeed, we have known for a long time, from purely clinical observations, that some urinary constituents, like urea and sodium chloride, are excreted almost proportionately to the volume of the urine; and that others, on the contrary, like uric acid and phosphoric acid, are not influenced by the quantity of urine. In order to examine this problem in a quantitative way, a series of observations has been made by my assistant and collaborator, Otto Loewi. These experiments were made on dogs and rabbits in the following manner: The normal excretion of uric acid, urea and phosphoric acid was studied during a preliminary period of several hours. In still other cases the excretion of sugar was studied—indeed, not merely in diabetes following pancreas extirpation, but also after phlorhizin administration and intravenous injections of sugar. Then the secretion of urine was increased experimentally through free administration of water or by means of diuretics, such as sodium nitrate or caffeine, and during the diuresis so induced the above-mentioned constituents were quantitatively determined. Finally similar observations were made during and after the period following the cessation of the diuresis. The outcome was that the excretion of urea and of chlorides ran regularly parallel with the volume of the urine. On the other hand, there was never observed any parallelism between the excretion of water, on the one hand, and the increased amount of uric acid and phosphoric acid normally produced in the organism, on the other. I specially emphasize the phosphoric acid normally produced in the organism, for any phosphoric acid introduced as a salt into the circulation showed a different behavior. Such introduced salts followed the same law of excretion as the chloride and urea; and this same general law held true in the case of sugar.

The blood, as is well known, always contains sugar, but in a combined form, so that the sugar under normal conditions is not excreted by the kidneys. But after pancreas extirpation or after an intravenous infusion of sugar in normal animals, the sugar content of the blood rises above the normal; the greater part of it can not exist in combination in the blood but is free and, like urea and other crystalloids, is excreted by the urine. And it appears from Loewi's experiments on diuresis that in such pancreatic or infusion diabetes, the quantity of excreted sugar was always proportional to the volume of urine excreted. In phlorhizin diabetes, on the other hand, the behavior was entirely different. As you are aware, there occurs no hyperglycaemia in phlorhizin glycosuria. There is no increase of free sugar in the blood, but the normally combined sugar is liberated from its combination and excreted from the kidneys. And this specific cellular sugar excretion was shown to be quite independent of the filtration of fluid through the glomeruli, that is independent of the amount of diuresis. From this it seems to follow, in fact, that the substances which exist free in the blood pass out mechanically with the water; while other bodies, such as uric acid, phosphoric acid, phlorhizin-sugar, and probably the urinary pigments, are excreted from the kidney by special secretory activity. It is not necessary that a substance exist in a crystalline state in order that it be secreted by mechanical filtration through the glomeruli; it may equally well be a colloid, provided,

however, that it is not combined with the blood tissue. It has long been known that dissolved hemoglobin and injected albumin passed through the kidney into the urine. It is also shown by direct microscopical investigation that these bodies pass through the glomeruli. And, as in the case of urea and salts, this excretion of proteids through the glomeruli has been shown by experiments by Dr. Schmidt and Dr. Loewi in my laboratory to be a mechanical filtration.

This specific excretion of uric acid, etc., can not be increased by any of the known diuretics. The action of diuretics, therefore, can surely not be explained by the supposition that there is a stimulation of the secretory activity of the kidneys. And, moreover, a specific renal secretion is something quite different from the secretory activity of the glands, for the typical glandular poisons, like pilocarpine, not merely are without influence on diuresis in general, but have no effect whatever on the excretion of uric acid, phosphoric acid, etc. If, then, the filtration of the watery constituents of the blood is highly probable, it follows that as a means of saving water there must be a compensatory resorption in the tubules analogous to the process of resorption from the alimentary canal. In the case of the intestinal tract large quantities of fluid are secreted from the mouth, stomach and small intestines, even to the amount of several liters in twenty-four hours, which is later reabsorbed in the large intestine, especially in the colon, resulting in the semisolid fæces. And a similar process may be conceived to go on in the kidneys.

We have undertaken to determine whether this conception is correct. If under normal conditions such a process of concentration occurs in the tubules, one would expect a diarrhœa (that is, a flow of unconcentrated fluid from the blood) to result from elimination of or injury to these parts, just as there results a flow of watery fæces if the colon be removed or its cells paralyzed by poisons, or if the contents of the intestines are rendered incapable of absorption by the addition of certain salts. With this thought in mind Ribbert long ago conducted experiments involving the removal of the medulla of the kidney, as a result of which he did, in fact, observe an increased secretion of a very dilute urine in rabbits. Similar experiments were undertaken by Dr. Hausmann and myself three years ago, by means of a somewhat modified operative technique and especially with the aid of quantitative analysis of the urine. In rabbits from which the right kidney had been removed previous to operation on the left kidney, we found the excretion of urine increased three or four times, just as did Ribbert, and observed a change from a concentrated mucus-like urine before the operation to a light-colored watery urine of low specific gravity after the operation. Quantitative analysis further gave the noteworthy result that whatever might be the normal content of chlorides and urea, after the operation the content always approximated that of the blood serum; for example, if the normal content of sodium chloride in a diet poor in this salt averaged 0.1 per cent. or in a diet rich in sodium chloride approximated 2–3 per cent., after the operation there would result in each case a percentage of sodium chloride which varied within the narrow limits of 0.6 to 0.8 per cent. This result seemed to speak strongly for the resorption theory. The resorption activity of the kidney may be influenced by pharmacological means as well as by removal of the uriniferous tubules. One would expect, as in the case of the intestines, that salts would check resorption from the tubules, and, further, that as in the case of the intestines, the

bibasic would act more strongly than the monobasic salts. Comparative study of the action of Glauber salt and common salt injected into the blood vessels, made by Dr. Halsey, yielded the expected results. Results similar to these unpublished ones, have been obtained by Gottlieb and Magnus of Heidelberg, and especially by Cushny, of Ann Arbor. The isosmotic solution of Glauber salts possessed a much more strongly diuretic action than common salt. From these experiments we may conclude with Cushny that the salts prevent water resorption from the tubules and set up a kind of diarrhœa in proportion to their power of withdrawing water, and that hence in accordance with the Ludwig theory, we must assume that a resorption of water occurs under normal conditions. The matter is, however, not quite so simple, for the salts, owing to their ability to withdraw water, also withdraw water from the tissues into the blood, thereby increasing the filtration stream through the glomeruli. Cushny further showed that fixed constituents, like sodium chloride, may be reabsorbed, as in the case of the intestines, by the epithelia of the tubules, that the difficultly diffusible Glauber salt was only slightly and slowly reabsorbed, and that finally urea is apparently not reabsorbed at all. A further striking example of such a renal diarrhœa, as I am inclined to call it, has been brought forward by Loewi. As I have already stated, every diuresis dependent on increased glomerulus filtration occasions also an increased excretion of sodium chloride and urea. If one poisons an animal with phlorhizin there also occurs an increased diuresis. This phlorhizin diuresis, as Brodie showed, appears to be wholly independent, in general, of the circulation and especially of the circulation through the kidney. And, what particularly interests us here, this diuresis is not dependent on the filtration of water through the glomeruli, for, according to Loewi's analysis the chlorides and urea were not excreted in increased amount, as is the case in all the other forms of diuresis. The phlorhizin diuresis must be regarded, therefore, as a pure tubular diarrhœa, brought about by the sugar excreted in the tubules of the kidney itself and there hindering the resorption of water by means of its water-attracting properties.

We have, therefore, in many instances two closely connected processes which constitute the basis of increased diuresis, the interference with resorption from the tubules, and the increased filtration through the glomeruli, the latter being probably the more important factor. The question arises what are the conditions that determine the operation of these factors? It may be that to a slight extent the diminished viscosity of the blood or, more properly, the degree of saturation of the colloids of the blood with water are here concerned. We know that in thirsting animals the kidney secretion can not be increased in any way; we have, therefore, no quantitative conception of the extent of this influence. On the other hand, we know of one factor which is of determining significance for the process of filtration. This is the blood flow through the kidney. It was long ago shown by Roy that as a rule every diuresis is associated with an increase in the volume of the kidney, that is, sets in simultaneously with an increased blood flow, and the experiments of Roy have been repeatedly carried out with essentially the same results by numerous investigators, and especially by Gottlieb and Magnus and by Starling and Bayliss. Still it appeared from time to time that there were exceptions in which increased diuresis occurred in association with an unchanged volume or scarcely perceptible increase in the volume of the kid-

ney. Gottlieb and Magnus, therefore, felt justified in concluding that the increased blood flow through the kidney is not the primary and determining condition for increased diuresis, but rather a regular and not essential associated phenomenon. My collaborator, Professor Loewi, also carried on a large number of experiments in this direction. He, too, found that in certain cases the oncometer showed no increase in the volume of the kidney, notwithstanding an increase in diuresis. We further undertook to determine whether diuresis occurred under the influence of diuretic agents, like caffeine and salts, even when the volume of the kidney was fixed so that an increased blood flow is presumably prevented. For this purpose the left kidney of the rabbit in a relatively quiescent and relatively anemic condition was encased in plaster of Paris with the exception of the hilus only, so that an increase in the volume of the kidney was wholly excluded. The surprising result was obtained that even in the case of such rigidly enclosed kidneys, diuretics like caffeine and salts were able to induce an abundant diuresis. Hence it seemed to be actually true that an increased filtration may be induced without any increase in the blood flow through the kidneys. But more careful investigations showed that the volume of the kidney is by no means a certain measure of the blood flow through this organ, but that the volume of the kidney and the blood flow through it may be independent. For by inspection of the outflowing venous blood it could be seen that, notwithstanding the rigid limitation in the volume of the kidney, the flow of blood through the organ was always enhanced during diuresis. While the blood which flowed through the renal vein was dark previous to the diuresis, the stream took on a light, arterial color under the influence of caffeine and salts. The mere fact, therefore, that the kidney does not increase in size in some cases of caffeine diuresis is no proof that the process of diuresis does not depend on an increased flow of blood through the kidney, and one may say that an increased renal blood flow is a regular and essential condition of diuresis from salts, urea and caffeine—a condition wholly sufficient, in itself, to explain the diuresis. It is not possible to say with certainty whether in the case of caffeine diuresis there is also a diminished resorption of fluid through the urinary tubules, as Sobieranski's experiments appeared to show. Another important fact was brought out by Loewi in this connection; we know that every hydremia, whether induced by the administration of water or by the withdrawal of water from the tissues by means of salts intravenously injected, gives rise to an increased diuresis, without any increase in the general blood pressure or the work of the heart. What is the origin of such a diuresis? Loewi found that every hydremia, whatever may be its origin, acts upon the vessels of the kidney as a specific excitant, in that it dilates the vessels and thus causes an increased glomerular filtration. Thus we have obtained an explanation for the increased secretion of urine arising from all forms of hydremia, from the drinking of water, and from the withdrawal of water from the tissues, in consequence of the action of the diuretic salts. Hence we may say that all the observations that have come to us by physiological and pharmacological methods harmonize with the conception that the water of the blood and the free crystalloids therein dissolved are liberated from the glomeruli by the process of filtration or perhaps a process better described as transudation, and, further, that the urinary tubules reabsorb, by means of their epithelial cells, not only water, but also, in

cases of salt poverty, sodium chloride as well (these being materials which the organism can not afford to lose), while at the same time these epithelial cells, like those of the intestines, have also to perform the duty of excreting the combined substances of the blood by means of their specific secretory activity.

Diuresis, therefore, represents the fusion of two principal processes—one concerning the gomeruli, which is in its main features mechanical in its nature; the other pertaining to the urinary tubules, which is not yet explicable on any physico-chemical hypothesis. The process of resorption from the urinary tubules has a distinctly biological, that is, teleological character; water and salt are only reabsorbed when the organism does not possess these in excess. If one administers an abundance of water, the urine acquires a highly watery character, while after the administration of an abundance of sodium chloride there is a failure on the part of the tubules to reabsorb salt, as Loewi has shown. The process of reabsorption adapts itself, therefore, to the requirements of the organism.

Although I believe that the theory of renal function which I have here presented is the one which has the best experimental foundation, I readily concede that it leaves many facts still unexplained. For example, it is difficult by means of this hypothesis to explain the constitution of the urine in diabetes insipidus as well as the complete retention of chlorine under certain conditions, and I fancy that we shall have to suppose, as Cushny has done, that there is some kind of combination of sodium chloride with the blood tissue which hinders its filtration. The theory of diuresis and the action of diuretic drugs further possesses a practical interest. If, for example, it be true that caffeine acts diuretically through local specific dilation and not through irritation of the secretory cells, as was formerly supposed, then, as Loewi thinks, we are justified in its administration during long periods in the course of nephritis in which, in many instances, the vessels of the kidneys are abnormally contracted. And there is some reason to believe that the vasodilator action of the caffeine not merely induces an increased diuresis but exerts a favorable influence upon the pathological condition of the kidney itself.

In conclusion, I desire to express my appreciation of the courteous attention you have accorded me. HANS MEYER.

THE EVOLUTION OF SPECIES THROUGH CLIMATIC CONDITIONS.

IN a recent article in SCIENCE,[1] entitled 'The Origin of Species through Isolation,' President David Starr Jordan has presented much evidence bearing upon the influence of geographical isolation in the formation of species and races of animals and plants. He dwells especially upon the agency of barriers in interrupting the flow of life and isolating groups of individuals of a species, which groups of individuals, either with or without material change in the conditions of existence, 'may become in time an entirely distinct species if the barrier is really insurmountable.' This is impliedly recognized as only one of various influences that tend to modify species, but in this connection, in marshalling the evidence in favor of the proposition of the origin of species through isolation, hardly any reference is made to the part played by other agencies in the evolution of new forms. In this way, rather undue importance is given to a single and well-recognized factor in the problem of evolution. The purpose of the present paper is not to

[1] N. S., Vol. XXII., No. 566, November 3, 1905, pp. 545–562.