Section of Urology.

President—Dr. W. Langdon Brown.

The Influence of the Endocrines on the Work of the Kidney.

PRESIDENT'S ADDRESS.

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I REGARD the honour of my election to the chair as a recognition by the Section that urology has a medical as well as a surgical aspect. One must admit that of recent years it is the surgical aspects that have shown the most advance, and that the surgeons have taken the most interest in the work of the Section. I therefore appeal to my fellow physicians not to lag behind but to emulate the good example of the surgeons.

I have chosen for my address the relation of the endocrines to the work of the kidney because it gives me the opportunity of bringing forward a view of the biological position of the endocrine system which has interested me of recent years; and of considering this more particularly in relation to the regulation of the excretion of water by the kidney.

The primitive excretory organs, as we find them in the invertebrates, are nephridia, typically segmental organs opening internally into the body cavity and externally on to the surface. At first they are all alike, as in the worms and that primitive arthropod *Peripatus*, but in the more specialized arthropods they have become differentiated according to the region of the body in which they lie. The most anterior group become condensed into the green gland of the Crustacea which still retains an excretory function. On Gaskell's theory of the origin of the vertebrates from arthropods, the old alimentary tract, of which the infundibulum represents the mouth, became the central canal of the nervous system. In the Crustacea the gills keep up a vigorous current of water from behind forwards, so that waste products discharged in this situation are speedily carried away from the animal, whereas in the fish, with the current going in the reverse direction this would lead to contamination of the water supplied to the gills. Circumstances alter function, and a new use was found for the gland in this position; it became the pituitary. Comparative morphology points to the conclusion that in the neighbourhood of the gill-slits, segmentally arranged structures give rise to the tonsils, thyroid, parathyroids and thymus, in the position which might be expected if they are homologous with nephridia, and on Gaskell's theory they represent the modifications of the second group of nephridia. It will be noted that two of these are now lymphatic in structure while the others are glandular. Now in both the invertebrates and the lower vertebrates part of a nephric tubule may become

converted into lymphoid tissue, which shows its association with excretory functions by taking up into its leucocytes alizarin blue and carmine which have been injected. A nephridium may thus differentiate in two directions. But it may become modified in yet a third direction. The position and arrangement of the uterus in *Limulus* closely resembles that of the thyroid with its thyroglossal duct in *Ammocoetes*, the larval lamprey, one of the most primitive of the vertebrates. Not only is the presence of this duct thus explained, but as Gaskell says, "the relationship which has been known from time immemorial to exist between the sexual organs and the thyroid in man and other animals, and has hitherto been a mystery without any explanation, may possibly be the last reminiscence of a time when the thyroid glands were the uterine glands of the paleostracan ancestor." We may also have an explanation here of the close association between tonsillar sepsis and thyroid enlargements if both structures originated from segmental nephridia. Coincident enlargement of the thymus with that of the tonsils or of the thyroid is capable of a similar explanation. These glands have become ductless because of the modification of the appendages to which they were originally attached. This modification became necessary because the formation of a new alimentary tract, ventral to the nervous system, closed their original outlet to the surface. Further down the body in the Elasmobranch fishes there is an unpaired series of interrenal glands in close connexion with the kidneys. These were considered by Weldon to be derived from mesonephric tubules (later observers suggest they are pronephric), and by Swale Vincent to represent the cortical part of the adrenals. The Elasmobranch fishes also show a paired series of chromaffin glands derived from sympathetic ganglia. Higher in the scale these separate elements coalesce, and the main mass of the chromaffin glands forms the adrenal medulla, becoming surrounded by the interrenal tissue as the cortex. This striking union of two structures of such widely different origin as the cortex and medulla of the adrenals must have an important advantage because once it was achieved in evolution it was never dropped. While if it fails to occur in fœtal life, the brain remains in the fish stage, the neopallium does not develop, and an anencephalic monster results. I would suggest that the success of an adrenal graft into the testis in Hurst's case of Addison's disease might have been due to its insertion into a tissue of similar origin, the adrenal cortex and the interstitial cells both arising from the Wolffian body, which is of nephridial origin.

It may be asked why the excretory functions, originally so uniformly distributed in segmental nephridia, have become restricted to such condensed structures as the kidneys. It is doubtful whether the tubules of the vertebrate kidney are strictly homologous with the nephridia of invertebrates although so similar in structure and function. Nephridia arise as invaginations from the exterior, and are, therefore, epiblastic—while their lumen is intracellular, i.e., is tunnelled through the cells. In the lower vertebrates the kidney tubules grow out from the body cavity and are therefore mesoblastic—while their lumen is intercellular.

Of the embryonic nephros which arises from the Wolffian body only the hindmost part, the metanephros, becomes the functioning excretory organ. The duct of the pronephros becomes the oviduct, and that of the mesonephros the vas deferens. This was formerly regarded as an annexation of kidney ducts by the gonads, but recent work points to the opposite conclusion, that the functional kidney has been split off from primitively gonadal tissue. In the higher vertebrates it is questionable whether the functional kidney is

formed from the Wolffian body, as, like nephridia, it arises by epiblastic invagination, but unlike them, the lumen of the tubules is intercellular and never opens into the body cavity.

All this points to three interesting and distinct phases in the evolution of the excretory system. First, the epiblastic intracellular nephridia of the invertebrates which open into the body cavity; secondly, the mesoblastic intercellular kidney tubules of the lower vertebrates shut off from the body cavity; thirdly, a return in the higher vertebrates to the process of epiblastic invagination but not to an intracellular duct nor to a communication with the body cavity.

Although this is not yet completely proven, I understand that the opinion of biologists at the present time is tending to accept this view. It is an extraordinary example of the way in which nature can change her plans according to circumstances, and can construct organs *de novo* which resemble the old ones closely enough to have deceived biologists for more than a generation. It shows how plastic is the evolutionary process, and that it is not so dependent on recapitulation as we thought. Further, it throws fresh light on the alliance of gonadal and excretory functions in the genito-urinary system. It offers fresh fields for exploration as to the relationship between the gonads and the adrenal cortex.

I wish to suggest that the influence of the endocrine glands on the kidney is in part, at least, the expression of the interest they continue to take, as it were, in functions which were formerly their own. Macallum[1] maintains that the earliest function of the kidney was not so much the elimination of waste products as the regulation of the inorganic composition of the blood. While nephridia opened into the body cavity the external medium of the sea and the internal medium naturally tended to be closely similar. But with the shutting off of the nephridia from the body cavity by the intrusion of a vascular tuft the animal was set free from the tyranny of its external medium, could individualize its metabolism, as it were, and change its habitat without altering the conditions under which its tissues and organs worked. This independence of external media is far more characteristic of the vertebrates than of invertebrates, and the change from nephridia to kidneys has thus been of special importance in the evolution of vertebrates. This independence is maintained even when a mammal returns to marine life, so that whereas the oceanic forms of invertebrate life tend to have the same saline concentration as the sea, the whale retains very much the blood salinity of the pig. The development of a circulation which enabled excretion to be adequate even when confined within a small compass was an important factor in rendering this change possible. When nephridia were replaced by a more adaptable mechanism and some of their outlets were dammed up by the formation of new structures such as the vertebrate alimentary tract and the pleural folds, they either had to vanish altogether or to take on some new function. To a large extent the second course was adopted and some of them became endocrine glands. The internal secretions may be looked upon as specializations of the old chemiotactic mechanisms and they reveal their antiquity in the way they cling to vestigial structures. Not infrequently, when in the course of evolution a structure has become useless for its original purpose the endocrine system supplies it with a new tenant. This change of function is illustrated by the adrenal cortex, thyroid, thymus, pituitary and pineal glands. They remind us of the hermit crab that seizes on an empty whelk shell. And just as the

[1] Macallum, *Proc. Roy. Soc.*, 1910, Ser. B. lxxxii., pp. 602-624.

hermit crab existed before it found an empty house, so the endocrine functions were in existence, in a less specialized form, before they had a local habitation. It is one of the merits of Gaskell's theory that it explains many of these points. All of these structures, except the pineal, represent modified nephridia. And I doubt whether the pineal is an endocrine structure at all, but should agree with Llewellys Barker that in disease it acts by disturbing the basal ganglia rather than by a direct secretory effect.

As we see vestigial remains of excretory structures in the endocrine glands, so there are vestiges of excretory methods in internal secretions. The active principle of thyroid secretion is an iodine compound of indol, which is a decomposition product of tryptophane, a constituent of the protein molecule. Indol is ordinarily split off by the intestinal bacteria, so that it looks as if we were dependent on these parasites, particularly *Bacillus coli*, for the first step in the preparation of an important hormone; one, indeed, which is essential to adult development. During the nursling period the infant gets its thyroid secretion from its mother's milk, and during that time the *Bacillus coli* is hardly ever present in its bowel. The suckling child has not a very active pancreatic secretion, and therefore cannot split off tryptophane very easily from protein and thus does not form indol to any extent.

This would fit in very well with Herter's views as to a form of infantilism due to persistence of the intestinal flora of the nursling period. It would appear that the body can not only detoxicate indol by converting some of it into indican, but can actually change it into a defensive substance. This would explain McCarrison's observations on the influence of intestinal intoxication on thyroid enlargement. It is reminiscent of the primitive excretory functions of the thyroid to find indol conjugated with iodine in its secretion, while indol conjugated with potassium sulphate continues to be excreted as indican by the kidney.

It is also interesting to note that tyramine, which is produced from the putrefaction of tyrosin in the human alimentary canal, is closely similar in chemical structure and action to adrenalin. It tempts one to refer the formation of adrenalin to the tyrosin of food proteins, just as thyroxin arises from tryptophane, another aromatic group in food protein. But it should be noted that the body is capable of making its own tyrosin, and that in alkaptonuria, a congenital error of metabolism, although the body is unable to utilize the tyrosin of the food, symptoms of hypo-adrenalism do not occur. Nevertheless, I anticipate that further research may show that other endocrine secretions are modifications of excretory products, just as endocrine glands are modified excretory structures. Other hints are to be found in such things as the diuretic effect of thyroid extract by dehydration of the body fat; the destruction of a purin body such as guanidine and the regulation of the calcium ions in the blood by the parathyroids. To sum up this part of my argument, Macallum's theory may be restated, that the principal function of the primitive nephridia was to bring the internal working of the organism into harmony with its environment. Now surely this is exactly what the endocrine system continues to do, both through its secretory activity and through its close association with the emotional, i.e., the sympathetic nervous system. In this way a further division of labour is achieved, the kidney being set free from the labour of forming an internal secretion, and able to devote itself entirely to excretion. But at the same time we should expect to find that the other internal secretions would be able to influence the work of the kidney in order to ensure harmony between the internal economy and its environment.

This is particularly well seen in the persistent relationship between the pituitary and the kidney. This is of biological interest because the pituitary represents a gland which was definitely excretory in function in invertebrates as high as the crustacea, and is of clinical interest as bearing on diabetes insipidus and polyuria in general.

It would generally be agreed that polyuria is due to one of the following causes :—

(1) Increase of the quantity of fluid imbibed.

(2) Increase in the molecular concentration of the urine, as in diabetes mellitus or after saline diuretics. More water is thereby attracted into the blood-stream from the tissues by osmotic pressure.

(3) Incapacity of the kidney to excrete a concentrated urine, as in chronic interstitial nephritis.

(4) High blood-pressure, which tends to force more blood through the renal vessels.

(5) Dilatation of the kidney vessels, as produced by stimulating diuretics of the caffeine group.

In addition to these recognized causes, there is the condition of diabetes insipidus the cause of which to some extent is still a matter of dispute. I wish to discuss its pathology to see what light it throws on the work of the kidney in relation to polyuria in general. It is clear that several different conditions have been thus described. Erich Meyer, in 1905, described a type dependent on a primary defect in the kidneys, which are incapable of secreting urine of normal concentration, so that a much larger amount of water is needed to remove the ordinary products of metabolism. This would place the disease in the third category of my classification, but, personally, I should not include it in the category of diabetes insipidus at all. Meyer found that in this type 20 grm. of sodium chloride would cause a marked diuresis, whereas the normal kidney can respond by secreting a more concentrated urine. Yet in spite of diuresis the excretion of the salt would be delayed, even for days. This condition resembles interstitial nephritis in that particular, for the minute trace of albumin would be hardly recognizable in such a large amount of fluid.

Indeed the post-mortem records of some cases diagnosed as diabetes insipidus strongly suggest that the patient really suffered from chronic interstitial nephritis. When Saundby stated that in diabetes insipidus the cause of death might be a gradual destruction of kidney substance, producing uræmia, he was evidently describing this type of renal insufficiency.

Meyer introduced an interesting test for recognizing this condition. Theocin sodium acetate increases the permeability of the kidney, and when this permeability is diminished for solids, this drug, by facilitating their excretion, does away with the necessity for further dilution of the urine. Hence, though it ordinarily acts as a diuretic, here it merely raises the concentration of the urine without increasing the output of fluid. Now in the cases of ordinary diabetes insipidus in which I have tried this test, theocin sodium acetate did act as a diuretic ; in one case the daily output rose from 5,000 c.c. to 8,000 c.c. as the result of giving 2 gr. of the drug twice a day. On the other hand, in a case of polyuria, which I concluded was one of Erich Meyer's type, the drug did not have a diuretic effect. The patient was a boy of seven and I investigated him five weeks after symptoms began. His output of salt was delayed though that of iodide was normal. His urea concentration was very poor, being 0·5 per cent. before the test and never rising above 0·6 per cent. afterwards. Yet the blood urea was normal, showing that with an output of 3,175 c.c. he was

able to prevent urea retention. There was generally a trace of albumin present in the urine. I re-investigated him three years later, and I shall have occasion to refer to some of the results later on. He was clearly suffering from renal insufficiency and as he had developed very little in the three years that elapsed between my two observations he recalled the type of renal infantilism described by Morley Fletcher, except that he had no rise of blood-pressure. Rabinowitch has shown that in ordinary diabetes insipidus, unlike chronic interstitial nephritis, the power of concentration is quite good for nitrogen. Which confirms the distinction I am drawing.

It will be realized that restriction of the ingested fluids is a futile and cruel procedure in the renal type of case. The condition of the kidney necessitates polyuria and if fluid is not given, then the patient must obtain it from his own tissues. He loses weight and the output of nitrogen rises, showing that the deprivation of water is producing a breakdown of tissues. This increased excretion of nitrogen in turn demands greater excretion of water. The appetite and general health will soon suffer, while the distress from thirst becomes extreme. An attempt to restrict fluids in this case, which was made before he came under my care, resulted in the boy drinking any dirty water he could find, and even his own urine.

It is well known that a syphilitic meningitis at the base of the brain can produce the symptoms of diabetes insipidus, especially in children. The Wassermann test is therefore imperative in every case, even when there are no stigmata of syphilis, congenital or acquired. An example of the latter cause in an adult came under my observation. A woman at the age of 40 married for the second time; two years later she suddenly began to pass 25 pints of urine a day. The Wassermann reaction was strongly positive. She improved on antisyphilitic treatment and valerian, but two years later the reaction was still strongly positive, although the quantity of urine had fallen to 9 pints. The thirst and polyuria were certainly better when she had valerian as well as mercury and iodide. This was before the days of treatment by pituitrin injections. Her tissues remained fat and flabby throughout, as is the case in some cases despite the high grade of polyuria. This is in itself suggestive of hypopituitarism. The nearer the meningitis is to the interpeduncular space, the more apt is it to excite diabetes insipidus, though this in itself does not enable us to decide whether the pituitary or the nervous tissue of the hypothalamus is really responsible.

Frank disease of the pituitary body may certainly be associated with persistent polyuria. The association of pituitary tumours with diabetes insipidus has been recognized since 1882. Primary optic atrophy, bitemporal hemianopsia and some form of ophthalmoplegia may occur in diabetes insipidus, pointing to the pressure in the region of the pituitary. In 1898 Bousfield reported three consecutive cases of diabetes insipidus with primary optic atrophy. In 1912 Frank recorded the case of a bullet-wound involving the posterior fossa which produced diabetes insipidus; he collected eighty-five cases of bitemporal hemianopsia, in eighteen of which this disease was present. Fractures at the base of the skull often excite a transient glycosuria and may induce a more prolonged polyuria. In a case of pituitary tumour operated on by Cushing, incomplete decompression was followed by unquenchable thirst, with polyuria reaching twelve litres a day. Several observers, among whom I may mention Bailey and Bremer, maintain that here as in the other group of cases, it is not the posterior lobe of the pituitary which is itself at fault, but that it acts by irritating the nervous tissues of the hypothalamus and tuber cinereum. Indeed

Bailey and Bremer regard the hypothalamus as an important head ganglion of the visceral nervous system, thus making the condition depend directly on the sympathetic.

It will therefore be convenient to consider next the cases of diabetes insipidus in which there is no evidence of syphilitic meningitis, pituitary disease or renal incapacity. The polyuria is then sometimes regarded as secondary to polydipsia. But in that case it ought by gradual and systematic reduction of the intake to be possible to reduce the output to normal, even though at the cost of much discomfort to the patient. This is not what occurs, for a point will be reached at which further restriction of the intake will not be followed by a fall in the output, which still remains abnormally high. Buttersack believes that when the unrestricted intake exceeds the output the condition is due to a primary polydipsia, but even here I have not found it possible to reduce the output to normal. In such cases I have found a negative Wassermann and a normal skiagram of the pituitary fossa. Theocin-sodium acetate did not reduce the output of urine, and salt was readily eliminated, though a saltless diet diminished thirst. Glycosuria excited by the injection of phloridzin appeared and disappeared in the normal time. Valerian diminished both thirst and polyuria. This is a point which can be determined by direct observation and we should not be deterred from the use of this drug because it has sometimes been used irrationally or because absurd explanations were formerly given of its mode of action.

The three types of diabetes insipidus due to syphilitic meningitis, frank pituitary disease and the so-called primary form, show remarkable resemblances to one another, and a sharp contrast with the renal incapacity type. It is therefore reasonable to suspect a common cause and to look for that cause in the pituitary. It is tempting to assume that even in the "primary" type there is some nervous or toxic disturbance of the pituitary when we know that drugs such as valerian, codein and pituitrin can help all three forms. Nervous tics between the medulla and the pituitary through the curiously indirect course provided by the sympathetic have been described by Cushing, Weed and Jacobson, but Dixon failed to find that any form of nerve stimulation caused any change in the secretion of the pituitary. Yet some structural or secretory change in the posterior lobe affords the most plausible explanation of diabetes insipidus, of the temporary polyuria after some head injuries and perhaps even of hysterical polyuria.

But are we to postulate an increased or diminished action of this lobe? The diuretic effect of pituitrin described by Schäfer and Magnus in 1901 has been proved by later observers to be quite transitory. Indeed, most of the earlier experiments must be discarded because allowance was not made for the complications introduced by anæsthetics. Farini in 1913 was the first to show that injections of pituitrin diminished polyuria and this effect has subsequently been repeatedly demonstrated in the normal man and in patients with diabetes insipidus.

That a toxic influence on the pituitary may produce diabetes insipidus is shown by the following case under the care of C. H. Miller. A young officer was admitted for diabetes insipidus following some pyrexial attack at Salonika. He passed about 590 oz. of urine a day and drank a corresponding amount of fluid. The Wassermann reaction was negative, and there were no signs of pituitary tumour. Miller noted a thrombotic condition of the saphenous vein over the internal malleolus which he had found more commonly in typhoid and paratyphoid fevers than in other conditions. The

vein was hard, rigid and solid like a tendon, the same condition extending back along the branch communicating with the deep veins among the calf muscles. He therefore had a stool examined, with the result that paratyphoid B organisms were found in pure culture. He concluded that diabetes insipidus had been started by paratyphoid fever, the patient now being in the carrier stage of the disease. He then tried the effect of pituitary extract, and found that great improvement followed immediately. The urinary output fell to 200 oz. on each occasion. Miller's suggestion is that there was a partial interference with pituitary function as the result of paratyphoid. In some cases of diabetes insipidus the associated symptoms also point to hypopituitarism. Motzfeldt (*Endocrinology*, 1918, ii, p. 112) has reported three instances of this association, and the persistent obesity which I have several times seen in spite of profound diuresis in the disease seems to me to support this contention.

We may next inquire at what point pituitrin normally acts in its control of diuresis. It does not interfere with the absorption from the bowel, for as Priestley (*Journal of Physiology*, vol. lv, 1921, p. 305) points out, diarrhœa is not provoked as one would expect if large quantities of water remained in the bowel, particularly as pituitrin stimulates the intestinal musculature.

It does not act through the vasomotor system, since it is equally effective on the denervated kidney,[1] and no obvious effect on the renal circulation was noted by Priestley. Indeed, Priestley's experiments in which an injection of pituitrin delayed the onset of diuresis by four to six hours, during which the ingested water was stored up in the tissues while dyes such as phenol red could still be excreted in a concentrated form, point to some direct inhibitory action on the renal tissues. This view is also taken by Addis. Oehme (quoted by Priestley) expresses the action of pituitrin as inhibiting the sensitiveness of the kidney to hydræmic stimulus. I should agree with Rabinowitch in regarding diabetes insipidus as due to the lack of some internal secretion which normally regulates and moderates diuresis by acting on the cells of the kidney, and I look upon pituitrin as that secretion. The output of the pituitary may be diminished either by structural or toxic damage and possibly by nervous causes. In connexion with nervous factors I should like to refer again to the view of Bailey and Bremer that it is not the posterior lobe of the gland which is at fault but the nervous tissues of the hypothalamus. Surely it is extraordinary in that case if there is an anti-diuretic hormone produced in close anatomical relation to the hypothalamus yet having no physiological relation with it. Is it not more probable that any influence of the hypothalamus exerts itself through the pituitary? This would explain the apparent contradiction that while nervous factors obviously influence diuresis, the effects I have been discussing can be demonstrated in the denervated kidney. It would be but one more example of the influence of the involuntary nervous system upon the endocrine system.

It seems to me that we can express the situation most concisely by saying that *pituitrin regulates the threshold of the kidney for water*. This would account for the apparently aberrant instances of a diuretic effect of pituitrin. It would also explain its selective action on water while not hindering the output, for instance, of dyes.

The materials excreted by the kidney fall into two categories, according to Ambard: (1) Those which are purely waste products and useless to cellular life, such as urea, ammonia, and uric acid. There is no threshold for their

[1] Bailey and Bremer, *Arch. Int. Med.*, 1921, xxviii, p. 773.

excretion. Most drugs are excreted in this way. (2) Those which may play a useful part in cellular life, such as sugar, sodium chloride, hæmoglobin and water. The kidney interposes a threshold in the way of these, so that they only pass into the urine when their level in the blood exceeds this barrier. But the barrier is not kept at a constant level. The variations in the height of the threshold is one of the ways in which the kidney adapts itself to contingencies. Water is clearly a substance of value to cellular life. So is sugar, and all recent work on glycosuria has served to emphasize the importance of the variable threshold in this condition. Thus we have in hyperthyroidism a clear instance of an endocrine disturbance, which leads to a marked rise of the threshold for sugar. I should regard a high blood sugar curve without glycosuria as typical of hyperthyroidism. Indeed, the word "threshold" conveys a very inadequate idea of the situation. A sluice, which can be raised or lowered as required, is a far more exact simile. And this sluice can apparently be controlled through certain endocrines. It can be made to vary for one urinary constituent without involving another. And thus the endocrines can influence the work of the kidneys in a subtle way. It has been suggested also that the calcium drainage in the ketosis of diabetes is due to failure of the parathyroids, which coöperate in some respects with the pancreas, but I do not know of any evidence that this is due to an alteration of the kidney threshold for calcium.

But the matter is not without its difficulties even on this view. Thus the experimental evidence as to the relation between the pituitary gland and the cerebro-spinal fluid is somewhat contradictory. Why should lumbar puncture produce such a striking effect for a time in diabetes insipidus? We have all seen it, and Herrick[1] in one instance reduced the urinary output from 11,000 c.c. to 600 c.c. by merely withdrawing 5 c.c. of cerebro-spinal fluid in this way. Is it possibly due to relief of pressure on the hypothalamus? One can hardly suppose such a slight relief of pressure on the pituitary itself could produce such an effect. Dixon[2] has shown that pituitrin normally passes into the cerebro-spinal fluid, yet Marenon and Gutierrez,[3] while agreeing that pituitrin is antidiuretic, failed to find any evidence of an oliguric hormone passing into the cerebro-spinal fluid. In this connexion it is interesting to recall that Douglas Cow found the diuretic effect of water absorbed from the bowel to be greater than if it were injected subcutaneously. On the theory here adopted this would suggest that something absorbed from the bowel with the water diminished the output of pituitrin—a sort of antisecretin. But Dixon in repeating Cow's experiment found that a boiled and filtered extract of intestinal mucosa actually caused a secretion of pituitrin into the cerebro-spinal fluid after a latent period of one to two hours. It is really very difficult to reconcile all these discrepant results. Pituitrin is certainly anti-diuretic under clinical conditions; it appears to pass into the cerebro-spinal fluid, yet no oliguric hormone is found there. Water absorbed from the bowel is more diuretic than water injected subcutaneously, yet a substance can be extracted from the intestinal mucosa which actually increases pituitary secretion in something over an hour, whereas by hypothesis the secretion of the gland should be diminished. Evidently the experimental evidence requires repetition. Kennaway and Mottram have postulated the presence of both

1 *Arch. Int. Med.*, 1912, x, p. 1.
2 *Journ. Physiol.*, 1923, lvii, p. 129.
3 Quoted by Hall, *Amer. Journ. Med. Sci.*, 1923, cxlv, p. 560.

diuretic and anti-diuretic principles in the pituitary. I think it safer merely to say that the pituitary regulates the output of water by some direct effect on the kidney cells, and that at present we do not know exactly how it strikes a balance between the water of the blood and urine. When present in considerable excess its oliguric effect is certainly the predominant one. On the current theory of urinary excretion, this action of pituitrin would promote re-absorption of water by the renal tubules, thus concentrating the urine.

It is quite conceivable that when the output of water tends to fall a small quantity of pituitrin may stimulate the glomeruli of the kidney, causing mild diuresis, but that when the output is greater a larger dose of pituitrin may stimulate the tubules, thus causing them to concentrate by re-absorption. Such reversible actions are familiar in the case of catalysts. But this is merely speculation in the present state of our knowledge.

Finally, I should like to point out that a large dose of pituitrin has an anti-diuretic effect not only on the normal subject and the patient with diabetes insipidus but also on the Erich Meyer type of renal insufficiency. I have already said that in this type the concentrating power of the kidney is impaired for solids, which is not the case in ordinary diabetes insipidus. A dilute urine is necessary, yet here, too, pituitrin can hold up the output of water. Thus, in the example of this type I have already referred to, Graham and I found that although the injection of $\frac{1}{2}$ c.c. of pituitrin had no effect on diuresis 1 c.c. would check it for sixteen hours. Three years later we repeated the observation with a similar result. It was recently stated by Blumgart that intranasal spraying of pituitrin would produce a similar effect on diuresis to that produced by intramuscular injection. I have certainly found this an effective way of relieving the headaches of hypopituitarism. We therefore tried the spraying method in this boy's case. An antidiuretic effect was obtained, though not so marked as that obtained by injection. On a fixed intake of 2,000 c.c. there was an output of 4,300 c.c. without any pituitrin. By spraying this was reduced to 2,850 c.c., while after injection it fell to 2,250 c.c. The conditions were not perhaps stictly comparable. For the nasal method one uses a solution of pituitrin only half the ordinary strength, and it is not practicable to administer 2 c.c. of this, intranasally, at a single sitting. Half a c.c. was therefore given three times a day. Now it had previously been shown in this case that 1 c.c. in a single injection produced an effect, whereas $\frac{1}{2}$ c.c. would not. It comes to this: the equivalent of $\frac{3}{4}$ c.c. of ordinary pituitrin given in three doses intranasally reduced the output by 33 per cent., (i.e., at the rate of 44 per cent. per c.c.), while 1 c.c. given intramuscularly reduced it by 48 per cent. This supports the efficacy of the intranasal method. But it also shows that an adequate dose of pituitrin controls excessive diuresis whether the pituitary is or is not at fault, and therefore does not really lend support to the theory of pituitary deficiency as the cause of diabetes insipidus.

Nevertheless, on a review of the whole evidence, I would suggest that so-called idiopathic diabetes insipidus may be due to some affection of the hypothalamus which interferes with the normal control of the threshold of the kidney for water, not through the vasomotor system but through the pituitary gland.

I would summarize my conclusions thus: Claude Bernard urged that the object of all vital mechanisms was to keep the internal environment constant. We have seen that nephridia originally were the principal means of maintain-

ing a constant relationship between the internal and external environments. In evolution nephridia were replaced by analogous but probably not homologous tubules which form the kidney, the function of which may be defined as that of keeping the chemical composition of the blood constant. Some nephridia were retained and modified to house the hormones, which, previously less specialized and more widely distributed, now play an important part in maintaining the internal environment. Haldane will not allow that they are to be regarded as something *sui generis*. He says "The truth is that every substance which enters into the life processes of any part of an organism is as much a hormone as any other such substance. Water, for instance, is the most abundant constituent of the body, and a very minute excess in the diffusion pressure of water in the blood excites very striking reaction in the kidney."[1] But while it is, of course, true that to a certain extent every product of cell activity has an effect on every other tissue, I think it is, nevertheless, convenient to place in a separate category substances having such specialized actions as the recognized hormones.

Not only morphologically but physiologically these modified nephridia recall their origin. The last of them to retain excretory functions, the pituitary, still shows its association with such functions by the profound modification it is able to exert over the threshold of the kidney for water. It is probable that diabetes insipidus is due to a loss of this control, and it is possible that the overlying nervous structures influence the matter through the pituitary; they certainly can do so without the intervention of the vasomotor system.

[1] "Respiration," 1922, p. 387.