A Post-Graduate Lecture

ON

THE HUMORAL SYNDROME OF GOUT.*

BY

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In addressing you to-day I wish, in the first place, to thank you for the honour you do me in inviting me to take part in this conference. I see in it a promise of excellent relations of friendship and scientific intercourse which will unite our two countries more and more. But you must allow me to say also that it is not without hesitation and apprehension that I have made the choice of the subject with which I propose to deal. Am I not a trifle overbold to come and speak on gout here in England, where Sydenham wrote his immortal description of the acute attack of gout—a description always copied or imitated, but never equalled; where Bright taught us to recognize the gouty kidney; where Scudamore and Gairdner wrote their classical dissertations; where Garrod inaugurated the scientific study of gout in demonstrating the pathogenic rôle of uric acid; and where so many eminent clinicians have since proclaimed the results of their investigations of this disease? My excuse is that in science nothing is final or perfected, and I shall have achieved my object if I awaken your interest in the new researches which for nearly two years I have conducted in my clinic at Saint-Antoine with my two co-workers, P. Brodin and A. Grigaut.

It is necessary in every study of gout to return to Garrod; his book has not passed out of date, and is rich in information, in clinical experience, and in personal ideas. It was Garrod who first defined the humoral state in gout and recognized and proved its essential character—excess of uric acid in the serum. I am bound to recall the delicate test of the thread, with its crystalline deposits of uric acid. In spite of the fact that this technique seems not to be exact, since we cannot say that all the uric acid of the serum becomes deposited on the thread, Garrod was able to estimate the quantity found in 65 grams of serum, which in the five cases he quotes, when expressed in terms of 1,000 grams of serum, give the figures 50 mg., 125 mg., 30 mg., 175 mg., and 110 mg. A little farther on, for the blood of patients suffering from albuminuria or gout, he gives an average quantity of uric acid varying between 44 and 173 mg. per 1,000 grams. He is careful, however, to add that in all these analyses the quantity of uric acid obtained is undoubtedly less than the real figure. The limit of sensitiveness of the method is fixed at 24 mg. per 1,000 grams of serum.

It is very curious to note how Garrod's technique gave him results near to the figures which we obtain at present with improved methods. Results of absolutely the same order are obtained in both cases.

These ingenious researches of Garrod's are classical, and all clinicians have made use of the thread test. But this obviously imperfect process did not allow fresh progress, and whilst researches on the uric acid of the urine were multiplying we relied on the initial researches of Garrod for the uric acid of the blood. A new technique was necessary, and it came to us from America with the work of Folin and Denis, and the employment of the reagent phosphotungstic acid, which gives a blue colour with solutions of uric acid. The estimation, which was gravimetric in Garrod's method, has thus become colorimetric, and the researches of Lough, Fine, and Myers have brought new and interesting deductions.

According to the American technique the normal content of the serum in uric acid is estimated at 2 to 3 centigrams per 1,000 grams, rather a low figure on account of the solubility in water of the precipitate of urate of silver and magnesium, which diminishes the real figure of the uric acid of the serum.

In the technique modified by A. Grigaut this cause of error no longer operates, and we believe ourselves to be able to say that the normal figure of uric acid per litre of the serum varies between 4 and 5 centigrams; hyperuricaemia commences above this.

Grigaut's process estimates the uric acid without including the xanthin bases, and only alloxan and alloxanthin, derived from the immediate oxidation of uric acid, are included with this substance in the figures of the estimation. Setting out

in this way we were able to begin the study of gouty uricaemia, and the researches we have published¹ were carried out in the first place on thirteen gouty individuals, and we studied for each the level of the blood urea, of the uric acid, of the cholesterinaemia, and determined the urea secretion constant of Ambard, which is the most delicate means we possess for appreciating the degree of renal permeability. Our results are summarized in the following table.

TABLE I.

Diagnosis.	Blood Urea.	Ambard.	Uric Acid.	Cholesterin.
Chronic gout	0.40	0.10	0.127	2.95
Acute gout	0.40	0.80	0.115	2.15
Chronic gout	0.33	0.10	0.122	2.25
" "	0.30	0.13	0.118	2.85
" "	0.33	0.08	0.118	2.07
" "	0.43	0.08	0.11	1.86
Acute gout	0.34	0.09	0.10	2.10
Chronic gout	0.35	0.13	0.10	1.65
" "	0.45	0.10	0.10	1.50
" "	0.45	8.12	0.09	2.15
" "	0.40	0.11	0.087	2.70
" "	0.40	0.11	0.078	1.80
" "	0.72	0.11	0.072	2.00

To this first series of cases I am able to add fourteen new cases, some observed at Contrexéville by M. Schneider, with estimations performed by Grigaut, the others derived from my hospital or private practice. Here are the results:

TABLE II.

Diagnosis.	Uric Acid.	Cholesterin.
Gout and uric acid lithiasis	0.10	2.07
Chronic gout	0.095	2.25
" "	0.085	2.13
" "	0.075	3.60
" "	0.069	3.25
Mild gout	0.065	1.86
" "	0.070	3.50
Biliary lithiasis and mild gout	0.06	2.70
Chronic gout	0.17	2.60
" "	0.10	1.89
" "	0.73	—
" "	0.11	1.80
" "	0.06	2.40
" "	0.07	1.98

The average for all these figures gives for 27 cases 0.094 of uric acid, and for 26 cases 2.25 of cholesterin in the serum. On the other hand, in a case of juvenile hereditary gout studied during the crisis and immediately afterwards, we have found a lower series of figures—namely, 0.24 for urea, 0.023 for uric acid, and 0.82 for glycaemia. Only the cholesterinaemia was increased to 1.95, and the bilirubin of the serum was in excess. In this case Ambard's constant stood under the normal at 0.06, and perhaps the exaggerated permeability of the renal filter was the cause of the low figure for uric acid. Hyperuricaemia was not present, but the participation of the liver was evidenced by the high level of the cholesterinaemia and by the excess of biliary pigment in the serum.

Thus the hyperuricaemia, discovered by Garrod, is confirmed and made more precise by modern researches. But whence arises this excess of uric acid?—a very complex question, and one still beset with uncertainty. In the first place let us differentiate between endogenous and exogenous uric acid.

For the endogenous uric acid we must distinguish two sources. On the one hand there is a disturbance of nitrogenous metabolism—and this is the factor we know least

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about in spite of the number of researches which have been devoted to it. There seems no doubt that uric acid is derived from nucleo-proteins and purins of the tissues by a series of degradations, due probably to the action of proteolytic ferments, the uric acid, according to Lambing,² "representing in man the end-product of the metabolism of purins—that is to say, a waste product which the organism does not further simplify." But the endogenous origin of the purins in the gouty, and their nature and manner of variation, still remains a mystery—as, for example, in cases of early hereditary gout, where the exogenous cause plays no part.

On the other hand, there is a second cause of endogenous hyperuricaemia of which the frequency and significance are easily understood—namely, renal retention. We know by clinical experience how often the kidney is damaged in the gouty, not only as a contracted and sclerotic kidney, but almost from the commencement of the illness there may be a functional defect betrayed by the elevation of Ambard's constant, as in our cases. This is only a secondary effect in the morbid process; but it ought never to be lost sight of without clinical consideration of hyperuricaemia. The retention of uric acid may even precede the retention of urea, and we believe ourselves able to say with P. Brodin and A. Grigaut that the detection of the former constitutes the most delicate test of commencing renal hypo-permeability.

Probably side by side with renal retention we ought to give a place to tissue retention, the gouty depositing uric acid in the tissues in excess, and being able to liberate it and return it to the circulation under the influence, for example, of causes producing acute attacks. This process does not appear to me to participate except in special cases, and its importance is not comparable to the uric acid retention of renal origin.

With regard to exogenous uric acid, for a long time the results of clinical observation have borne witness, and all are aware of what a large share in the causation of gout is attributable to errors of diet, to food in excess, too protein in constitution, too rich in spices, and to alcoholic beverages, notably burgundy and champagne.

The determining factors of the hyperuricaemia of alimentary origin are probably to be attributed directly to the excess, together with the secondary modifications in the nutrition and metabolism of the tissues and hepatic activity dependent thereon.

But here arises a question which cannot be separated from this discussion—namely, the rôle of the liver in gouty hyperuricaemia. The clinicians have for a long time admitted the capital importance of the part played by the liver, and the work of Scudamore and of Garrod on gout, and of Murchison on the functional disturbances of the liver, had led to the supposition that the liver manufactured uric acid when, on account of illness, its urea-forming function failed. On the other hand, the physiologists admit that in mammals uric acid and purin bases are destroyed whilst passing through the liver by uric-acid-splitting ferments. We have turned to experiment, in order to elucidate this point, by taking samples from the portal and hepatic veins of dogs for the estimation of uric acid during digestion and under various dietetic régimes. The following table illustrates our results:

TABLE III.

No. of dogs.	Régime.	Blood.		Coefficient of retention in liver.
		Portal.	Hepatic.	
1	Fasting	gr. 0.087	gr. 0.00.7	0
2	"	0.011	0.011	0
3	"	0.015	0.015	0
4	Milk	0.006	0.006	0
5	Varied	0.007	0.009	0
6	Brain	0.010	0.003	20
7	Calf's sweetbread	0.0118	0.009	23
8	Varied	0.034	0.025	27
9	Calf's sweetbread	0.031	0.022	30
10	Varied	0.018	0.011	39
11	"	0.015	0.010	34
12	Liver and spleen	0.014	0.007	47
13	"	0.013	0.006	53

Studying the details of these experiments we see that five dogs received a varied diet, two were fed on calf's sweetbread, and two with liver and spleen. The results obtained were all similar, and in eight of the nine dogs the quantity of uric acid in the hepatic blood was markedly less than that of the portal vein. Once only was the hepatic content a trifle higher than the portal—9 mg. in place of 7.

The proportion of uric acid retained varied between a minimum limit of 20 per cent. and a maximum of 53 per cent., with an average of 33 per cent.

The variability experienced in the retention coefficient must be attributed to many and special causes for each case: differences in the anatomical and functional condition of the liver in dogs of varying kinds; different stages of digestion; the nature of the food given.

The two highest figures of retention—47 and 53 per cent.—were obtained in animals fed exclusively with liver and spleen, a diet rich in uric acid. On the other hand, in three dogs maintained in the fasting state for three days, with as much water as desired, the content in uric acid was exactly the same in the portal and hepatic blood. The same result was obtained in a dog fed on milk, a diet which contains only traces of uric acid. Thus in the dog during the digestive period a greater or less proportion of the uric acid substances brought by the portal vein is retained by the hepatic cells, the liver playing the part of a regulating organ, designed to prevent the passage of excess of uric acid into the blood during the very frequent variations of the human dietary. We are ignorant of the fate of the uric acid thus retained, and we can only suspect that there occur in the hepatic cells complex chemical transformations of which we know one—the formation of urea. It is very probable that the fabrication of urea, the "protéopexie" of F. Widal, and the uricolysis are only different episodes, fragmentary evidences of the manifold action of the liver on protein material, all the stages of which we are far from knowing completely. This uricolytic function is periodic and only exercised under special circumstances, and it is very striking to observe the failure of this retention action in dogs in the fasting state, when the liver, no longer exerting any digestive control, allows itself to be traversed like an inactive gland. A milk diet which only supplies to the liver minimal traces of uric acid, and which throws least work on the digestive apparatus, acts in the same way as fasting, and fails to produce any difference in the uric acid content of afferent or efferent liver blood.

But it is a rule in general pathology that all physiological function has its counterpart in the pathological, and that the disturbed function can be deduced from the normal. Thus it appears permissible to state, in spite of the fact that direct proof cannot be given, that in the hyperuricaemia of the gouty the arresting function of the liver may prove insufficient, being incapable of retaining uric acid brought from the alimentary canal, and we might find in this the physiological explanation of the capital importance of diet in the gouty. Thus would also be explained the connexion which clinical experience has so long demonstrated between disturbances of the general nutrition, of the nitrogenous and carbohydrate metabolism, and functional disorders or lesions of the hepatic gland.

The uricolytic insufficiency of the liver thus appears to me to be one of the most important factors in the causation of exogenous hyperuricaemia of alimentary origin, and perhaps it may be passed on by inheritance—a possibility which would enable us to understand these cases of early hereditary gout, cases which cannot be explained as due to the life of the individual, and which can only depend on the transmission of an inherited defect.

Doubtless this is only an hypothesis of which one can show no direct proof in gout, but, as we have seen, it finds support in experimental physiology and in the other unmistakable signs of hepatic origin such as the hypercholesterinaemia and the hyperbilirubinaemia. Does not the same apply to other pathogenic theories in which one reasons more by deduction and analogy than by direct experiment, which is so difficult to carry out in clinical practice?

What becomes of the uric acid stored up in the tissues of the gouty, and what is its ultimate fate?

A part is eliminated in the urine according to the general law of the concentrating power of the kidney which Ambard formulated. When once the kidney is injured in structure or function then the elimination of urine is affected and may not suffice for its task. Another part, by a process of vicarious elimination, is deposited in the diseased joints as sodium urate,

in the tophi, in the urate incrustations of slow atrophic nephritis, and these local deposits once formed are not capable of being moved; they remain in ineffaceable witness of gout.

In the blood the circulating uric acid is more accessible to our therapeutic resources, and it is this which we wish to influence by diet or by our remedial agencies. It is difficult to say exactly in what chemical form the circulating uric acid occurs, but it is probable that it is in a state of colloidal solution as sodium urate, and we shall see what is the interest of the question in relation to the pathology of the acute attack of gout.

Finally, it seems that in chronic gout there is a uric acid infiltration of the tissues which is capable of modification, particularly by spa treatment. Schneider, Bricout, and Grigaut³ thus explain the curious facts they have observed at Contrexéville. The blood uric acid of the cases of gout treated at this station instead of diminishing actually increases, as if the excess of uric acid in the tissues was mobilized, liberated, and returned to the circulation by the lavage, and then gradually eliminated by the kidneys. One or two months later there is found a remarkable reduction in the hyperuricaemia.

In order to complete the study of the serological nitrogenous metabolism of the gouty we must add that the level of the blood urea is generally slightly raised, although not often passing the physiological limits; this is illustrated by the figures in Table I. This is all that can be said at present of the origin and fate of uric acid in the gouty, and if many of the details are still hypothetical or obscure, perhaps the outlines of the main processes can be distinctly discerned. It was interesting to study the uric acid content of the blood cells at the same time as the serum. With the assistance of P. Brodin and A. Grigaut⁴ we have attempted to carry out this investigation, although we recognize that many of the associated factors are but ill understood. The same holds for the blood cells as for the serum; we are still unaware in what form the uric acid exists, for the chemical combinations must be very complex and perhaps variable and of colloidal constitution. In the healthy individual and in patients suffering from various diseases the average level of cellular uric acid appears to be 20 to 25 cg. per 1,000, though not indicating any definite connexion with the figures for the uric acid of the serum. The inconstancy and variability of the figures obtained only permit us at present to assign to the cellular uric acid a value doubtful and of secondary importance. It is otherwise in the gouty, and in the five estimations which we have had the opportunity of practising in the course of chronic gout we have found the level of the uric acid markedly raised, giving an average of 36 cg. per 1,000—that is to say, almost double. The proportion is the same for the serum, with an average figure of 9 to 10 cg., as compared with the normal average of 4 to 5.

Patients with gout are thus suffering from a double hyperuricaemia, both in the cells and in the serum, and the two surcharges of uric acid seem to be associated and proportional. The cellular hyperuricaemia is probably only a particular localization of the more or less diffuse impregnation of the tissues in the gouty.

This question of the supposed presence of uric acid in the tissues helps to solve another problem—namely, that of the clinical diffusibility of uric acid. Since uric acid passes into the urine by way of the renal filter it is therefore diffusible; but little was known of the conditions under which this occurred. Our experiments, carried out with P. Brodin and A. Grigaut,⁵ have shown us that in ascitic and pleural effusions, uric acid, like urea, is found in the same proportions as in the blood. On the contrary, it only passes in minute traces or minimal quantities into the cerebro-spinal fluid, in marked distinction from urea. Similarly, in experiments conducted with artificial dialysis it is found that uric acid passes much more slowly than urea. The diffusibility of the two substances is not therefore absolutely the same, neither clinically nor experimentally.

It was supposed that the hyperuricaemia was the only modification of the blood serum in gout. In reality the humoral syndrome is more complex, and, working with P. Brodin and A. Grigaut, we have added a new element, hypercholesterinaemia. It will be sufficient to refer to Tables I and II to see that this is the rule, and in fact in 26 cases in which the cholesterol has been estimated the average level of cholesterinaemia is 2.25 grams, a figure considerably higher than the physiological average of about 1.70.

Undoubtedly this hypercholesterinaemia may be due, in part at least, to suprarenal origin, when the kidney is more

or less affected in its eliminating function or in its structure. But the hypercholesterinaemia may be an initial fact and precede the renal lesion, since, as is demonstrated in Table I, we have shown it to coincide with a normal or only slightly elevated Ambard's constant, and consequently with physiological kidney function. In view of numerous experiences of this kind there is no necessity to presuppose an increased production of suprarenal cholesterol, and the hypercholesterinaemia seems to be of hepatic origin. This is confirmed by the fact that the albuminous coagulum obtained by the action of trichloroacetic acid on the serum often shows after some hours a blue coloration more or less well marked, a reaction which betrays excess of bilirubin in the serum.

This double evidence of hypercholesterinaemia and hyperbilirubinaemia discloses the injury inflicted on the hepatic functions in gout, and only verifies the special state of uricolytic insufficiency which we have described as the result of our comparative estimations of the uric acid in the portal and hepatic veins. And thus the capital rôle which the liver plays in the pathology of gout is confirmed.

On the other hand, in the course of our researches on hypercholesterinaemia, it seemed to us possible to evolve a law—the law of the local deposition of cholesterol when the serum cholesterol is increased in a definite and permanent fashion. In this way we have explained the pathogenesis of xanthelasma, of biliary lithiasis, and of the white plaques of the retina in patients with Bright's disease. Shall we find in the gouty a new confirmation of this law?

Note first of all that biliary lithiasis is far from rare in the course of gout—6 per cent. according to Bouchard—and this clinical affinity, which it is classical to emphasize, has only been explained up to the present by vague theories, such as Bouchard's hypothesis of retarded nutrition. On the other hand, it adapts itself very well to the theory of the origin of cholelithiasis from the hypercholesterinaemia, the theory which I have formulated. Hutchinson observed a case of xanthelasma on the eyelids in a patient suffering from chronic and hereditary gout; Dyce Duckworth reported on palpebral tophi very similar to xanthelasma in a case of gout, and in another case multiple tophi of the scrotum, the chemical and microscopical examination of which showed the presence of sodium urate and crystals of cholesterol. Loeper, in many cases of gouty hygroma, has demonstrated the presence of cholesterol. What is lacking in these early records is the chemical estimation of cholesterol and uric acid in the tissues or tophi examined, and, above all, the determination of cholesterinaemia. One cannot interpret the source and significance of the deposition of cholesterol without ascertaining the quantity of cholesterol in the serum. We have therefore searched for the presence of cholesterol in the unfortunately very rare tophi which it has been possible for us to examine. In three cases of gouty deposits in the helix we have only been able to carry out Liebermann's reaction on account of the small quantity of material we had at our disposal; it was strongly positive, almost of the same order of intensity as that obtained with the xanthomatous nodules. The murexide reaction was also positive in the case in which it could be carried out. In a case of tophus of the finger, removed for diagnostic purposes from a young man of 22 suffering from hereditary gout, and showing typical acute attacks since the age of 13, the cholesterol content of the fresh material expressed per 1,000 grams was 8.30 grams and for uric acid 2.90 grams. This case was also peculiar owing to the fact that the tophi of the finger had really undergone a fibrous change. I have published the clinical history and histology with J. Troisier.⁶

At the autopsy of a patient who died of acute uraemia following renal tuberculosis typical deposits of sodium urate were found at the level of the articular surfaces of the metacarpophalangeal joints, but no cholesterol was present. In a case of tophus of the heel estimation gave the enormous figures of 85.80 grams per 1,000 of uric acid and 21.30 grams of cholesterol. Cholesterol therefore appears to be a constituent element of gouty tophi, and this new fact might have been suspected from clinical examination alone. Nothing is more dissimilar in appearance than the pulp of a tophus and the gouty incrustation of a joint. The articular deposit is white as snow, whilst the pulp of a tophus is yellowish, the colour of pale fresh butter. Even viewed through the skin this butter colour of the tophus is easily seen. Chemical analysis accounts for this difference of colour, showing pure sodium urate at the level of the joints and a mixture of sodium urate and cholesterol in the tophi.

Thus in gout the liver contributes largely to the typical double adulteration of the serum, hyperuricaemia and hyper-

cholesterinaemia, and the tophus is only the external reflection of the humoral syndrome. It seems as though the tophus represents an effort of liberation on the part of the organism, a local deposit assisting in the elimination from the circulation of the excess of uric acid and cholesterolin.

In all that has preceded we have described gout in the static stage when compensation is complete; but what happens when it passes to the dynamic state as evidenced by an acute crisis? At the moment we can only reason by analogy, and we are reminded of the suddenness of onset of similar acute attacks of asthma, migraine, urticaria—all paroxysmal illnesses and allied to gout by certain clinical affinities.

Since the researches of Widal, Abrami, and Iancovescu we have come to look on these morbid crises as precipitated by a disturbance of the colloidal equilibrium, very similar to anaphylactic reactions, with special modification in the number and percentage of the leucocytes, of the blood pressure, and albuminoid content of the plasma. All these crises can cause local lesions such as the oedema of the skin in urticaria and eosinophilic excretion in asthma. I think that it is along these lines that we must search for the explanation of the acute crisis of gout. Perhaps in the first place, as suggested by the researches of M. P. Weil and Guillaumin,⁷ the uric acid is in the free state in the plasma, for the greater part at least, and in the combined state in the blood cells. Guillaumin's technique seems to permit this differentiation.

In whatever ill-defined and colloidal form it exists the excess of uric acid places the gouty in a state of unstable humoral equilibrium, which may at any time be imperilled or destroyed under the influence of divers disturbing causes—errors of diet, traumatism of joints, in particular of the great-toe, by fatigue or an ill-fitting boot, dampness and cold, and the seasonal changes to which the gouty are so sensitive.

Every gouty patient is sensitive to some disturbing agent or other, and there are those who cannot take a glass of champagne or burgundy without their having almost immediately an attack of pain in the toe. To the general sensitiveness must be added a local sensitiveness which causes the inflammatory process to light up always at the same point, creating thus true centres of uric acid crystallization.

If the disturbance of the humoral equilibrium is sufficiently intense the acute attack of gout flares up, and we can look on it as a true local shock, comparable to the shock of a migraine crisis. Latent sensitiveness of the gouty, provocative cause, and sudden shock in the affected area—these are the three periods of the course of gout, and we can compare the third of these to the local serological shocks which reproduce true local anaphylactic reactions, recently studied by G. Bouché and A. Hustin.⁸

In both cases there appears an active local vascular dilatation—vascular or sympathetic phase, "vasotropic shock" of Bouché and Hustin—to which is added the painful reaction of the sensitive nerves. But in the gouty the process is complicated by a specific local reaction, the deposition, or rather the local flocculation, of sodium urate in the region of the inflamed joint. Does there exist at the commencement of the attack the haemoclastic reaction so well described by Widal and Abrami? We do not yet know, and it would be very interesting, although in practice very difficult, to investigate the point.

However that may be, if this explanation of an attack of gout be accepted we are led to consider the uric acid present in excess in the serum of the gouty as a potential exciting cause, capable under the action of the provocative agent of determining a local and elective shock with urate flocculation; a process of this kind recalls the curious experiments of A. Lumière⁹ on barium sulphate, which in the molecular state of dispersion can be injected into the circulation without causing shock, whilst in the flocculated state it invariably gives rise to the symptoms of shock.

If one day the existence of this process could be demonstrated in gout we should have made a great step towards the explanation of the symptoms of an acute attack of gout. This will be the progress of to-morrow, the counterpart of the admirable work of Sydenham and of Garrod, who will always remain our guides in clinical gout, our undoubted masters in the study of this great humoral disease.

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A British Medical Association Lecture

ON

PYELOGRAPHY.*

BY

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[With Special Plate.]

LITTLE time was lost after Roentgen had discovered the penetrating power of x rays in applying them to the detection of concretions in the urinary tract; but it was not until 1906 that it occurred to Voelcker and Lichtenberg to take advantage of the cystoscope and ureteric catheter so as to fill up the pelvis of the kidney with a fluid opaque to x rays and thereby obtain a photographic outline of the shape of the ureter and pelvis of the kidney. The paper published by these workers received scant notice for a considerable time, and it was not until some years later that their idea was taken up seriously by a number of workers in various countries and developed to its full possibilities. From 1910 onwards I worked at this subject extensively at the London Hospital, and in 1913 I published a full account of what I had been able to achieve on the clinical side, accompanying this with an account of experiments on sheep's kidneys, showing what happened to colloid suspensions when injected into the renal pelvis under varying degrees of pressure, and pointing out certain dangers and difficulties and how to avoid them.¹ I also produced evidence that the injection of such fluids under proper safeguards does no serious or permanent damage to the kidney.

During the last decade the method has been employed more and more until it has become recognized universally amongst urologists as an essential factor in their work. Pyelography was one of the chief subjects for discussion at the 1921 Congress of the Société Internationale d'Urologie held in Paris; at that Congress it was agreed that the method had come to stay and was one that had been developed to a high degree of safety in the hands of competent urologists. Dangers which were at first encountered by too strenuous workers have been gradually eliminated, and in the course of time improved injection fluids were discovered that cast deep shadows without irritating the kidney substance. At first various preparations of colloid silver were used, and later such substances as silver iodide, thorium nitrate, and potassium iodide, but none of these proved to be ideal. The silver preparations did not always cast a clear shadow, except in very strong suspensions, and the other substances sometimes gave rise to toxic symptoms. In 1918 Weld introduced sodium bromide, a 20 per cent. sterilized solution for the kidney and a 10 per cent. solution for the bladder. This though not an antiseptic is non-toxic and has the merit of casting a very distinct shadow. Nevertheless, it is sometimes very irritating if injected into a bladder the victim of a chronic cystitis, and in such cases I find it better to use a 10 per cent. suspension of colloid silver.

Pyelography enables us to study exactly the surgical anatomy of the kidneys, ureters, and bladder before proceeding to operation or treatment in a way which has been compared to the giving of opaque meals in the x-ray diagnosis of disorders of the alimentary tract. In practice it is found to yield a more accurate account as compared with the opaque meal or enema, which are frequently open to doubtful interpretations, the surgeon often failing to find what he has expected after a study of the opaque meal pictures. In dealing with the urinary tract it is seldom that we fail to find the exact condition revealed by the pyelo-radiogram or cystogram, though considerable experience is needed in interpretation of

* Delivered before a joint meeting of the Nottingham Medical Society and the Nottingham Division of the British Medical Association on March 15th, 1922.