of the pyrexia was 4.0 days; 103.6° F. was the highest temperature recorded. In most of the cases the thermometer did not rise above 101°. The pulse was quick, but examination of the heart revealed nothing beyond hurried action, nor was there any other sign or symptom found to suggest a rheumatic origin for the condition of the throat. In a few cases patches of transient non-punctate erythema capriciously distributed over the trunk and limbs were observed. In one case a thick crop of herpes developed on the chin. Though albuminuria might have been present at an earlier stage of the disease it did not recur at this period. The faucial exudation was almost always discrete, disappearing in a few days with or without syringing of the throat. In only one case was antitoxin injected, as the patches showed a tendency to coalesce. Three successive negative cultures proved that the angina was not diphtherial.

Owing to the aggravated form which serum manifestations assume when antitoxin has been administered afresh, after an interval of a few weeks, faucial deposit occurring late in convalescence from diphtheria as distinct from that designated angina redux, which usually requires no treatment, should be dealt with first by local measures. As will be seen from the above figures, the chances in favour of the tonsillitis being non-specific in origin decidedly outweigh those of its being due to a fresh attack of diphtheria.

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The Goulstonian Lectures

ON

AUTO-INTOXICATION: ITS RELATION TO CERTAIN CARDIO-VASCULAR DISORDERS.

DELIVERED BEFORE THE ROYAL COLLEGE OF PHYSICIANS
OF LONDON ON MARCH 13TH, 15TH, AND 20TH, 1906.

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LECTURE II.—[ABSTRACT.]

[AFTER recapitulating his first lecture as follows:

(1) That in 12 out of 68 clinical cases hypertension was observed, and that there was with one exception proof that the kidneys were affected in these cases; (2) that the explanation of hypertension in renal disease was unsatisfactory—a toxic cause had been invoked, but not demonstrated; and (3) that experimentally he had shown that a rise of blood pressure occurred eighteen times out of nineteen, in which kidney extract was used, and that such frequency of a pressor effect was not noticed after the injection of extracts of other organs—moreover, the pressor effect produced by kidney extract was a prolonged one—

Dr. Shaw gave an account of work carried out by Tigerstedt and Bergman ten years ago.]

They had set themselves the task of elucidating the relationship between kidney and heart, being influenced by the teaching of Brown-Séquard on "internal secretion," and by the association existing between certain renal and cardiac diseases. Their first experiment was rewarded by a successful result.

Freshly-excised rabbit's kidney was rubbed up with glass powder and physiological salt solution. The fluid obtained was then filtered, and a few cubic centimetres were injected intravenously into rabbits. In a short time a well-marked and apparently protracted increase of arterial pressure was observed. In the first experiment, within 80 seconds of the injection of 5 c.cm. of the extract, the maximal pressure had risen from 70 to 68 millimetres before injection to 102 millimetres—that is, an increase of pressure of about 50 per cent. had ensued; in a second experiment the increase after the injection of 4 c.cm. was 25 per cent. within 100 seconds; in

the third experiment there was an increase of 18 per cent. in 60 seconds.

The investigation was further elaborated. They found that extracts which were prepared by boiling the fresh kidney with water or extracts prepared from the boiled kidney by means of cold water were inactive. Alcohol, either absolute or of 50 per cent. strength, was quite unable to extract from the preparation any active material. They were also able occasionally, but not always, to demonstrate that diluted glycerine extract had a definite pressor effect.

One of the objections to the use of the extract which has been injected into the series of cats already referred to is that the material injected was a coarse emulsion, and that until this emulsion could be made to yield a soluble substance capable of exerting a pressor effect the results obtained could not be quite convincing. Tigerstedt and Bergman have, however, succeeded in obtaining a solution of the active material which can be quite freed from any granular contents.

The kidney is rubbed up with absolute alcohol and filtered; the precipitate is dried in the air at room temperature and is then extracted with salt solution; 1 to 2 c.cm. of this extract exert as great a pressor effect as the fresh preparation; the active substance is not destroyed by alcohol. They speak of this extract as "Extract A." If it is boiled or heated in a water bath this extract loses its properties, but exposure to a temperature of from 54° to 58° C. does not apparently disturb the pressor effect.

The pressure substance to which these workers give the name of "renin" is not dialysable. From these various reactions it may be concluded that renin is a substance *sui generis*, and that the effects produced on the blood pressure are not due to any of the crystallizable substances which are excreted in the urine. Further, "renin" was present only in extracts made from the cortex of the kidney, and not at all, or only to a slight extent, in extracts of the medulla. Other experiments suggested that renin actually passes from the kidneys into the blood; that in the kidneys a substance is formed which under normal conditions may pass from the kidney into the blood by a process of internal secretion, and may exert a pressor effect. A preparation of fresh extract made by rubbing up fresh kidney substance with fresh defibrinated blood was also found to be active. The result of the analysis of the effects produced by injection of "Extract A" was to show that fresh renal extracts produce rises of pressure by acting on the peripheral nerve centres as well as possibly on the spinal cord.

Finally, Tigerstedt and Bergman considered the question of the fate of renin when it enters the circulation normally, and concluded that renin is partly got rid of from the body by the kidneys, but that it is also partially destroyed by the body or is possibly got rid of by the bowel.

[After criticizing these experiments Dr. Shaw proceeded:]

It seemed well to endeavour to secure results under the most exacting physiological conditions possible, and so a limited number of further experiments were carried out, using renal extract for injection purposes prior to the injection of any other preparation.

The analysis of these results shows that on three occasions when the experiment was carried out, as in my first series, under the influence of ether only with spontaneous respiration a fall succeeded the injection of renal extract.

When anaesthesia was procured by the administration of ether and morphine, respiration being carried out artificially, a rise of pressure followed the injection of renal extract on 4 occasions. No rise, and even a fall, occurred in 3 experiments. Another condition was to administer ether and morphine or curare, to carry out artificial respiration, and to cut the vagi. A rise of pressure followed the injection of renal extract in 3 cases, and a fall occurred in 2 cases.

These results are obviously unsatisfactory, for although the majority give some support to the view that there is a pressor substance extractable from the kidney, a good proportion of cases show the reverse.

Pressor substances have been demonstrated in the suprarenal medulla and in the posterior lobe of the pituitary body, and there has been abundant confirmation of the results.

[Dr. Shaw then alluded to the experiments of Oliver¹ on the action of animal extracts on peripheral vessels.]

Oliver found no *invariable* change given by the use of extracts of liver, pancreas, kidney, or brain; a moderate constrictive effect, however, was obtained so far as the experiments had been carried out with extracts of spleen, testis, and pituitary gland. Suprarenal extract was found to produce a marked constriction which persisted for from thirty to sixty minutes.

[He then mentioned experiments by Lewandowsky, whose results were as follows:]

The injection of renal blood gave an effect differing in no way from that of the blood derived from the body—as, for example, out of the jugular vein. In three cases, however, there was a rise of pressure which was not inconsiderable, but Lewandowsky concludes it was not a specific rise, for the controls injected with jugular blood also showed a rise. He considers that in part this rise was due to the rapidity of injection, but admits that similar masses of saline solution injected under similar conditions were quite incapable of causing such a rise, and concludes that in defibrinated blood substances are present which, under certain conditions, can cause a rise of blood pressure. Whatever may be the verdict as to the value of Tigerstedt and Bergman's experiments in showing that there is an internal secretion in health, no one can doubt that the significance of their experiments with the renal cortex for pathology is very great.

The question that presents itself is, Can we derive from the observations of Tigerstedt and Bergman any explanation of the pathological departures which we have already noted as occurring in blood pressures at the bedside? The answer must be that there is good reason to think that they have added a great deal to our knowledge, because so far no one has been able to associate the alterations met with in the blood pressure in renal disease with any definite cause. If the renal cortex contains a pressor substance capable of causing rise of pressure, then when it enters the circulation, which it is reasonable to believe occurs in certain pathological conditions, blood pressure rises.

We know that in the contracted kidney one of the best-established changes is the shrinkage of the cortex, which has been shown to contain more renin or pressor substance than the medulla.

It is acknowledged that high arterial tension is not so constant a feature of chronic parenchymatous nephritis as of the interstitial variety, but still it does occur. It is, however, very common in cases of renal sclerosis. Possibly hypertension is an expression of a kidney condition in which renal parenchyma, little altered or not at all, is passing into the circulation either from changes, as in contracted kidney, associated with obliterative arterial disease or from toxic agents which are more common causes of parenchymatous changes. In cases of severe acute nephritis observations have been made with the sphygmomanometer which show that hypertension also occurs, and even may do so within twenty-four hours from the onset of the kidney lesion. It therefore seems probable that maintained hypertension may mean disintegration of kidney substance and its entrance into the circulation.

It is quite conceivable that some of the cases which are now being recognized as cases of increased arterial tension, largely owing to the help of the sphygmomanometer, without any signs of renal disease or of disease of the superficial arteries, are really cases similar to those just mentioned: a certain amount of renal sclerosis may be present and only show itself clinically by the production of increased pressure, by signs which are so slight as to be disregarded or so equivocal as to defy interpretation. Hypertension may be shown to exist in other cases when other organs than the kidney are undergoing disintegration; so far there is no evidence to show that clinically hypertension maintained for a considerable time exists, except in cases in which the kidney is affected.

The idea has been advanced that in uraemia a poison is developed which provokes arterio-spasm (Traube), and as a result of this condition such cases frequently present symptoms of monoplegia or hemiplegia, and yet *post mortem* no lesion can be found to account for such signs. Such a view would, however, require evidence that kidney extract can act directly upon the musculature of arteries, and so far this has not been shown.

That the blood pressure does not remain high in all cases of uraemia till death occurs does not militate against this toxic view of uraemia, because with the suppression of urine which so often occurs there is a retention of material which is able to act as a cause of lowered arterial pressure; and, moreover, as will be seen subsequently, one of the results of deep disintegration of tissues in general is to produce substances which cause constantly a fall of pressure.

There is reason to believe that the renal cortex when once it enters the circulation causes spasm of the arteries, acting as a toxic agent such as has been invoked by Traube, to complete his hypothesis that arterial cramp is responsible for some at least of the features of uraemia. If we invoke the teachings of treatment we find that this view is supported, for we know that renal asthma so-called, which is so often met with in sclerosis of the kidney, is able to be greatly remedied by the use of drugs which dilate the arteries. It may be that some of the signs of uraemia are dependent upon a sort of "intermittent claudication," or rather "paroxysmal claudication," of certain vascular areas, and that renin may be the immediate cause and local vascular disease a predisposing one; given the absence of either of these factors uraemia may not result, but it is possible to believe that the arterial spasm produced by renal pressor substance may in some cases be sufficient in itself to cause some of the phenomena of uraemia; that this is possible is to some extent shown by the fact that uraemia is not always fatal, recurring several times, and occlusive vascular disease may not be demonstrable in all cases.

Hypotension.—A consideration of the list of 68 clinical cases not only showed the existence of a group of patients in whom high arterial tension was a feature, but also a number in whom low pressure was present. The problem occurs, Is it at all likely that different effects are produced upon the arterial tension according to the degree of altered nutrition which exists in various organs in different diseases or in different stages of such diseases?

[Dr. Shaw then considered the phenomenon first seriously studied by Salkowski, auto-digestion—that is, a process in which the cell contents undergo liquefaction owing to their removal from the body, and so from their natural sources of food supply and from those means by which the products of their solution are able to be removed. Hoppe-Seyler in 1871 made the following statement: "All organs dying within the interior of the organism undergo, in the absence of oxygen or even in its presence, liquefaction; during the progress of softening leucin and tyrosin are formed from proteid and free acids or soaps from fats. The phenomenon is accompanied by no development of offensive odours and may be compared with the processes which are associated with the action of digestive ferments."]

Although these observations were made so long ago that the exclusion of bacterial effects could not have been considered, more modern work has proved the correctness of the view that tissues are able on their own account to liquefy. Hüfner, in 1872, made a discovery which brought the explanation of the process much nearer solution. He found that, after extracting the salivary glands of the pig and the lungs of calves by means of glycerine, it was possible by precipitation with alcohol to obtain a substance which differed very much from proteids, and was able to digest proteid. Thus digestive ferments appeared to be widespread in the system. It was, however, objected that such processes were entirely *post-mortem* changes, and that they had no representation in the living body—a somewhat singular attitude to adopt, for it is hardly to be expected, as Salkowski says, that when life ceased in the individual such a vital phenomenon as digestion of tissues should only then be initiated; it is much more likely that the processes operating after death are also active during life. Differences exist, of course, in the two conditions, for in life the primary dissociation products are removed, but in the dead body such products remain *in situ*.

Salkowski concluded that proteolytic ferments occurred not only in the digestive tract, but also were present throughout the body, and though weak agencies were necessary to the organism, for they were found in the lowest forms of life.

Analysis of the two preparations made by Salkowski showed that as a result of antiseptic autolysis there is a

considerable increase of soluble organic substances, and this is notably the case in regard to the nitrogenous bodies. The increase of soluble nitrogenous substances is due to the formation of primary dissociation products derived from proteids and nucleo-proteids.

It is well-known that the animal cell contains proteids in the cell body which also to some extent prevail in the nucleus, and that the nuclei contain various nucleo-proteids. Recent investigation in chemical physiology has been directed largely towards an elucidation of the cleavage of proteids and nucleo-proteids. These former bodies may be split by various agencies, such as heat, acid, alkalies, and bacteria, and then give rise to what are known as "primary dissociation products." But the same dissociation, which is a process of hydrolysis, being associated with the breaking up of water and the incorporation of the liberated hydrogen and oxygen, occurs in digestion of proteids and derivatives by the ferments pepsin, trypsin, erepsin, and arginase. The first two, especially trypsin, are instrumental in simplifying the proteids by producing albumoses and peptones, but also are able, though at a much slower rate of velocity of action, especially in the case of pepsin, to exert those deep disintegrations of proteid derivatives which are special duties of the erepsin and arginase ferments which are present, not only in the intestinal mucosa, but also in the tissues of the body, erepsin being almost universally distributed, and arginase being found especially in the liver.

[The lecturer then discussed the products of proteid dissociation, and especially the nucleo-proteids, and concluded his lecture as follows:]

By studying the effects on blood pressure of some of these derivatives, it is possible to draw some conclusions as to the possible causes of those interesting cases or occasions of depression of blood pressure which were noted in the list of clinical cases already referred to; the importance of such study is well shown by the observation that life is impossible when the blood pressure falls below a certain minimum.

REFERENCE.

¹ *Proceedings of the Physiological Society*, 1897, vol. xxii, p. 22.

MEMORANDA: MEDICAL, SURGICAL, OBSTETRICAL.

ACUTE YELLOW ATROPHY OF THE LIVER FOLLOWING INFLUENZA.

ACUTE yellow atrophy of the liver as a sequela of influenza is such an extremely rare event that we think the facts of the case are worth publication.

The patient, H. J., aged 31, first came under our care on March 3rd. His previous medical history was fairly good. He had indulged excessively in alcohol a few years back but not for a very long period. There was a history of gonorrhoea but not definitely of syphilis. He had suffered frequently from colic and spasms when a child, and had catarrhal jaundice in August, 1903, when he was ill for about six weeks. When first seen his temperature was 102° and pulse 112. He complained of pains in the head, back, and limbs, with a little cough. The tongue was furred and the mouth and pharynx dry. Influenza was diagnosed.

On Monday, March 5th, there was considerable bronchitis, moist sounds being heard all over the chest. The pyrexia gradually subsided until March 7th. On that day was first noticed a slight jaundice, and on the following day this was much more marked. The bowels were constipated; the urine contained no bile pigments, neither was albumen present. On March 9th, about 3.30 p.m., he had a convulsion. We did not see this, but from the description given were of opinion that a fit had occurred. About 10.30 p.m., when we saw him together, he had another definite convulsion—tonic followed by clonic spasms lapsing into a state of semi-consciousness. During the night there was considerable low muttering delirium. His state gradually developed into that usually known as "typhoid," with loss of control of the bladder, and semi-coma with short lucid intervals. The highest evening temperature at this stage was 99.2°. The jaundice became very intense on March 11th and 12th, the skin being quite bronze in colour. On March 14th he was seen by

Dr. Frank Nicholson of Hull, and the diagnosis confirmed. The liver dullness, which had been gradually getting narrower, was on this day absolute only for a width of 2 in. in the nipple line. The urine contained neither albumen nor bile pigments, but leucin and tyrosin crystals were found in abundance. The patient died on March 16th.

We regret that we were unable to obtain consent to a *post-mortem* examination, but the symptoms were so typical of the disease that we have no doubt that our diagnosis was correct, though one is always afraid to diagnose so rare a complaint.

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NASAL DEFORMITIES AND PARAFFIN INJECTIONS.

THE following case is a good example of the results which may be obtained by the use of paraffin injections in the redressments of disfigurements:

The patient, some years previous to coming under treatment, was kicked, whilst playing football, on the nose. A compound fracture of the nasal bones resulted, and necrosis of portions of the nasal bones taking place, the deformity shown in the first photograph followed. It was treated by subcutaneous injection of paraffin, performed in the usual way by Dr. H. C. Donald. The second photograph, taken a week after the operation, shows the result.

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PATENCY OF OESOPHAGUS RE-ESTABLISHED AFTER GASTROSTOMY.

FOUR months ago my colleague, Dr. Martin, and I examined a very cachectic man of 64 for oesophageal obstruction and increasing difficulty in swallowing; he could only swallow liquids with difficulty. Bougies were arrested 12 in. from the teeth. The larynx was unaffected. I performed a Ssabanejw-Frank operation without experiencing any difficulty, and for a month the patient was content to be fed by the fistula thus formed and made marked progress. He then suggested that he could be fed by the mouth with solid food. To appease his craving he was tried with liquid and then with fine minced meat. He then tried bread and potatoes obtained from other patients surreptitiously, and now can swallow and enjoy ordinary meals, though still weak and cachectic-looking.

Though highly satisfactory to the patient, this result is not easy to explain, except that by fastening the cone of stomach to the costal margin, the lower end of the oesophagus was pulled away from some growth behind it that was protruding upon it.

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TOBACCO POISONING IN A CHILD.

ON Good Friday last I was called in to see a boy, aged 2 years, whom I found to be in a dying condition from tobacco poisoning.

I knew the child well. He was a strong, sturdy little fellow, but it appears that recently his mother had come to the conclusion that "he had worms," and she was on her way to my surgery accompanied by the boy when a bona-fide midwife met her and assured her that she could cure him.