looking woman, with a clean skin, bowels regular, appetite returned, and felt markedly better.

In March, 1907, a sharp attack of abdominal pain followed by vomiting caused the diagnosis of perforated gastric ulcer, and a surgeon opened the abdomen; none was found. Recovery uninterrupted.

Since then she has been in excellent health and spirits, and now writes that she is quite well and thoroughly interested in and pleased with life.

CASE XLVII.—A single woman, who had suffered for years from severe constipation, and since 1905 had also passed mucus. This had been accompanied by great abdominal pain; her appetite had gone, and she had lost much weight. She showed marked signs of autointoxication.

In April, 1907, ileo-colostomy.

In January, 1911, her doctor writes that she is well nourished and looks well. Her colitis and constipation are quite cured. She has some abdominal pain still, and during an attack was seen by a consultant, who advised me to explore for gastric ulcer, which, however, I did not find.

She has been passing small uric acid stones from the right kidney, and this is associated with pain.

CASE XLVIII.—A single woman, who had suffered for years from extreme constipation, which had progressed, in spite of all treatment, up to an action once a fortnight. The act was accompanied by extreme pain, and was associated with left-sided abdominal pain, constant nausea, and attacks of vomiting.

In 1903 the abdomen was opened and a cystic ovary removed. Her condition became desperate; she was a yellow, sallow colour, markedly wasted, and at the end of her tether. For seven years she had been a complete invalid, and had scarcely been outside her house. At the time of the operation her condition was desperate.

In September, 1909, colectomy was performed, and the bowel was found firmly adherent, and a large mass of tuberculous glands was present, which involved nearly the whole of the mesentery of the small intestine.

In February, 1911, her doctor writes that "the improvement is really extraordinary. She has made a steady progress back to health. She is now quite plump again, and has put on a lot of flesh. She goes out and calls on her friends. She walks miles, and does all her housework. She is an entirely different person."

CASE XLIX.—A single woman, aged 40, had marked constipation for nine years, so that now by the aid of purgatives and enemata she averages one action a week. Frequent headaches. Constant cold hands and feet. Frequent abdominal pain. Is sallow and pigmented. Marked cystic changes in her breasts. She suffers from marked mental depression and inability. She cannot do any housework.

In August, 1910, an ileo-colostomy was performed, and she was discharged very markedly improved, much brighter mentally, her skin cleaner, vomiting and headaches gone. She is quite comfortable and feels much improved.

In February, 1911, she writes that she is still very pleased with her condition.

CASE L.—A man, aged 43, had always been inclined to be constipated. In 1898 he went abroad and had several attacks of dysentery with marked abdominal pain. He was treated by the greatest authorities, with only temporary benefit, and in August, 1906, soon after his return home was seized with haemorrhage and pain.

In January, 1907, an ileo-colostomy was performed with much difficulty owing to the anchored contracted condition of the rectum.

In March, 1911, his doctor writes: "The result of his operation has been excellent. Before it he was incapacitated by the frequent recurrent attacks of chronic dysentery. Since the operation he has had no trouble of this kind and has been able to return to work. I shall certainly recommend an operation if I have a similar case to deal with."

THE death of the life tenant having occurred, the Royal Victoria Hospital, Dover, has now come into possession of a large property known as The Shrubbery at Crabble Hill, near Dover. It was left to the hospital by the late Mr. Richard Coleman, together with a sum of money for its maintenance as a convalescent home.

DR. H. C. GROVES, who is about to leave the town of Monmouth after some twenty-four years of practice there, was the recipient on March 31st of a silver salver, a purse of 110 guineas, and an album containing an address and the names of over 600 subscribers. The presentation was made in the Rolls Hall by the mayor, who said that every man who did public work was submitted by the public to constant tests, which in the case of a medical man were of a particularly trying kind. He had to be genial, to be possessed of even temper; to be prepared to be called upon at any hour of the day or night; and to be ready to sacrifice the joys of life to a large extent in order to serve the public. Through all these tests, and many more, Dr. Groves year after year had passed unscathed, and thus had won the general esteem and admiration of the population amid which he had dwelt so long. Wherever he might go, he carried with him their very best wishes.

An Address

ON

ARTERIO-SCLEROSIS AND THE KIDNEYS.

DELIVERED BEFORE THE KENSINGTON DIVISION OF THE METROPOLITAN COUNTIES BRANCH.

BY

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(Continued from page 858.)

Bright's Disease and High Pressures.

OF the amyloid disease high arterial pressure is not a feature; but in acute parenchymatous nephritis and in acute interstitial nephritis, although in these maladies, and even in cases ending in recovery, the arterial pressures may rise suddenly to no inconsiderable heights and burden the heart severely, yet in them high pressures are of irregular and inconstant occurrence. Generally speaking, in England and in America, physicians from the time of Johnson and Wilks have divided chronic Bright's disease into Chronic Parenchymatous Nephritis and Granular Kidney, and the distinction is still recognized by Tyson* and Rose Bradford.¹⁸ All biological classifications are of course arbitrary, and divided by no hard and fast lines; but broadly speaking this distinction corresponds with clinical experience. In most cases the contrast of symptoms suffices to determine a diagnosis between the two kinds; and even in cases of doubt the difficulty of differential diagnosis probably lies more often in the data or opportunities of exact observation than in a blend of these morbid processes. Whether in particular cases the differential features may be conspicuous or not, Granular Kidney and Chronic Parenchymatous Nephritis are, each of them, a fairly consistent series throughout.

In the "Chronic Parenchymatous" clinical series, then, high pressures are by no means invariable. In this disease the heart, whether by dilatation or hypertrophy may be enlarged on both sides, if not to the same degrees; and in many necropsies no very great enlargement is notable. But in the granular disease the arterial stress, rising early and enormously, tells primarily and in the main on the left ventricle; dilatation of the right side being a late and secondary event, a condition of heart failure. Dropsy in granular kidney is rather cardiac than renal in nature. In respect of high arterial tension, then, in these diseases we have to do with variables as yet unappreciated.

Once more. As we may have chronic parenchymatous nephritis with high arterial pressure, or with comparatively little excess, or even with none, so conversely we may have high arterial pressures without any manifestation of renal disease. But in this important part of my argument I must tread warily, as I am entering into contested positions. Still, keeping as close as possible to accepted hypotheses, it is now generally admitted, I think, that Mahomed, v. Basch, Potain, Huchard, and myself were justified in declaring that high arterial pressures may and often do arise without renal disease in any accepted clinical sense—that is, without Bright's disease. Mahomed did suppose this increment to be a warning of Bright's disease, to be indeed a signal of its initiation; v. Basch and Potain took it to be a sign, and indeed a manifestation, not of Bright's disease, but of arterio-sclerosis. We have seen that Huchard, regarding arterio-sclerosis not as an anatomical result of several diseases but as itself constituting a disease, interpreted high arterial pressure as the first stage of it, and accordingly named this stage Presclerosis; as Mahomed, interpreting it as the first stage of Bright's disease, named it Prealbuminuria. My position, however, was this: that in the first place arterio-sclerosis was no unity, was not a "disease" in the clinical sense; and in the second place that although it was often associated with high pressures these were no necessary condition of it—a doctrine in which for some ten years I stood unsupported. Then

* In his valuable work on Bright's Disease and Diabetes.

Groedel contributed evidence of arterio-sclerosis without high pressures, an independence which now seems to be generally if rather tacitly admitted. Had Dieulafoy discerned the different relations of arterio-sclerosis in granular kidney, in hyperpiesis, and in vascular involution without high pressures, he would have been less puzzled by the inconstancy of parallel between the arterial and the renal changes. For even under the exorbitant pressures of Granular Kidney the distal arteries may long resist deterioration; a degree of immunity which I have attributed in part to the protection afforded by peripheral spasm—an opinion with which Dr. Harry Campbell agrees. Moreover, in persons under middle age at any rate, the arteries seem able to resist excessive tension, say for four or five years, without much injury; whatever minor spots and streaks may be visible in those of the larger magnitudes.* For so long, if there may become general fibrous increase of the intima, there is no splitting of the elastica, no subintimal hyperplasia. Indeed, as the cerebral arteries are among the first to suffer, the victim of granular kidney may die of an apoplexy while his large arterial trunks, whatever their loss of elasticity, are still in fair preservation.

In my Harveian paper of 1894, and again in the Lane Lectures of 1896, I stated accordingly that on eighteen years' experience of one case watched from first to last, and on a large experience of portions of many cases, a certain disease—that is to say, a fairly uniform series and correlation of symptoms positive and negative—is to be recognized and to be delineated, which, although marked from the outset by a rise of arterial pressures, does not follow the clinical course of Bright's disease in any of its modes, but manifests itself by other symptoms, not here to be described. Furthermore, that it is not an expression of arterio-sclerosis, but generally speaking, if recognized in time, is curable; and even if recurrent, as frequently it is, yet after two or three recurrences, by diet and other vigilant precautions, may usually be banished for good. If however, as too often is the case, it defies treatment, or is neglected, the arteries undergo such strain as to issue in arterio-sclerosis. I stated, further, that arterio-sclerosis is not itself a disease, but an event or result of several diseases; and that of itself it is not a cause of excessive arterial pressures, but on the contrary, from beginning to end, is quite consistent with ordinary pressures. It was to this disease, in origin independent of arterio-sclerosis, that I gave the name of Senile Plethora, or Hyperpiesis, meaning by Hyperpiesis not simply a character of pressure, but a certain morbid series taken as a whole—a series of which this rise is but one of the principal characters.

Of this malady I have never offered an explanation, or nothing more than conjecture; I have been content to distinguish it as a clinical series from the recognized forms of Bright's disease. I am far, then, from denying that in this disease of Hyperpiesis the kidneys may have some concern. Passing over the "renal inadequacy" of Clark as either renal disease or a vague speculation, I may mention here the argument of Dr. Batty Shaw, in his Goulstonian Lectures of 1906, an argument which I will discuss more fully later. He says—putting aside problematical instances in which changes usually tending to high arterial pressures are subdued by intercurrent conditions, such as cardiac insufficiency or competing toxins—it is agreed that the cases which Huchard and Allbutt, and before them Mahomed more or less, have separated from frank Bright's disease under such names as Prealbuminuria, Presclerosis, or Hyperpiesis, do not follow the common course of disease of the kidney; yet dependent upon renal disorder of an insidious kind they are nevertheless; furthermore, on a fatal issue, some defect in the kidney will be found. The pressor element in particular is of renal origin, and is probably due to an escape of renal substance, or products of renal dissolution—of nephrolysis, to use a current word—into the blood. Now this explanation may or may not be true; my concern is to point out again that the distinction lies between Bright's disease and a malady which, if caught in time, is, if not always, yet usually curable, and when incurable abuts upon cardiac defeat or

apoplexy, and does not at any stage even of a fatal career present uraemic symptoms; not, that is to say, anaemia, headache, nausea, lethargy, retinitis, convulsion, or coma. Hensen of Quincke's clinic (whose premature death is to be regretted) says: "I have convinced myself of this, that a blood pressure over 200 mm. may occur in cases of simple (*einfacher*) arterio-sclerosis in which clinical observation gives no support whatsoever (*keinerlei Anhalt*) to a diagnosis of renal disease." But Hensen had still to learn that in such cases even arterio-sclerosis is not a necessary factor. Whether in essence renal or not, the respective diseases—the fairly uniform series of symptoms, negative and positive—are widely different in course. And in the *post-mortem* room I demur that Dr. Shaw again does not draw a distinction between the atrophic or arterio-sclerotic kidney and the Granular Kidney technically so called, as do Professor Lorrain Smith and many other authors besides myself who believe the arterio-sclerotic kidney to be within limits still fairly capable, but who regard the Granular Kidney as corrupt, if not actively vicious from the beginning.

The slight and variable degrees or the absence of high pressures and cardiac enlargement in many cases of disease of the kidneys, even when their structure may have been impaired even to extremes, have for a long time been a puzzle to clinical observers. Some physicians have assumed that, if the heart is to be enlarged to any notable extent, besides the renal disease some correlated disorder of a systemic kind, vaguely indicated as a "cachexia" (Päessler,¹⁹ Senator), must be associated with the renal disease, a condition scarcely favourable to cardiac growth. Others, with doubtful success, have looked for the determining factor of the high arterial pressures in the differences of the renal elements concerned—as of the glomeruli, for example; or in epithelial decay; or in the quantity of renal substance abolished; or, again, in absorption of disintegrating renal substance. On one clinical distinction, at any rate, we are all agreed: namely, that the form of renal disease in which we find the arterial pressures constantly and regularly exorbitant, and the heart notably hypertrophied, is the "Red Granular," which form in this respect also is to be distinguished from other diseases ending in shrunken kidneys, such as the "small white,"† terminal or original. In these other processes, it is true, some arterial tension and cardiac enlargement are often found, but not so early, so constantly, nor so enormously as in the "red granular" form. As regards the amount of renal structure, that the cardio-arterial stress is not directly at any rate as the sum of its debility is apparent on comparison of red granular cases with cases of shrunken or damaged kidneys of other kinds in which the obsolescence of renal substance may in the sum be no less. In certain kinds of renal disease, such as the amyloid, in which the proper renal elements must be universally impaired if not obliterated, the heart may not be—in the amyloid is not—enlarged at all; nor the arterial pressures raised. And, when we look more closely at the red granular kidney itself, we find no definite relation between the destruction of the kidney and the rise of arterial pressures; the heart in these cases had often grown very large and the blood pressures very high before the disease had become manifest or importunate, or the urine much attenuated.

That Hasenfeld's hypothesis, which attributed the high pressures and enlarged heart to the geographical distribution of the arterio-sclerosis, namely, in the mesenteric area, had it been valid even for ordinary cardio-arterial hypertrophies and degenerations, is quite inadequate to explain the enormous cardio-arterial changes of granular kidney, has been proved by many observers; for instance, by the well-known researches of Marchand. I have said that Jores also in many cases of granular kidney with large heart and high arterial pressures had demonstrated that in the mesenteric area arterio-sclerosis was ill marked or virtually absent; and, indeed, that, speaking generally, the pancreatic, splenic, and cerebral arteries were, as a rule, more diseased than those of the bowels.

In thus turning our little lantern upon the correlations between high pressures, arterio-sclerosis, and renal affec-

* Recent transplantation experiments in animals to prove that high blood pressures do not injure the vessels seem to me to be very fallacious.

† Professor Bradford accepts the primarily contracting white kidney, indicating its often latent course in young adults. One or two of Jores, Prym and Roth's cases under the bundle name of *Schrumpfnieren* may have been of this kind.

tions, we see a crucial point, although we find no *instantia crucis*; we meet many another baffled inquirer, each perhaps with his own guess, or scrap of information, but no signpost. What are the scraps? Well, as we have seen, that in many cases of Bright's disease, or of tuberculous, or calculous, or surgical kidney, pressures do not rise at all; that in others the rise is not predominant, and does not affect mainly the left ventricle but both ventricles, and in the usual proportions, after the way of, and often because of, failing heart; inconsistencies in strong contrast with the definite class in which from the first high pressures are predominant, and, consequently, the left ventricle, in the manner of the so-called "concentric hypertrophy," is affected chiefly, enormously, and until the stage of cardiac failure, perhaps alone. Another scrap is that this constant and conspicuous cardio-arterial enormity is the mark not of any kind of Bright's disease, but of the disease to which we give the name of Granular Kidney.*

If not eminently characteristic of the rest, yet it is true that in other chronic renal diseases, even in "surgical kidney," a tendency to augmentation of arterial pressures is to be noted; so we presume that in the affections of the kidney there is a something which provokes this excess; something which in the granular kidney is a constant, in the others a variable. Is this something engendered in or of the kidney itself? In the view of Aufrecht, which a while ago found no inconsiderable favour, the granular kidney—the conspicuous example of this pressure-provoking agency—is but a local expression of arterio-sclerosis, the renal implications of which colour the whole malady. But, like Huchard, Aufrecht also regarded arterio-sclerosis as necessarily associated with high pressures, although in 1894-5 I had proved that very frequently it is not; and in particular that even an arterio-sclerotic kidney may be and often is associated from life to death with arterial pressures normal for the age of the patient. In 222 cases of arterio-sclerosis Dr. Mott found the heart and kidneys affected in 141 (82 male and 59 female), but in 30 male cases and 55 female neither heart nor kidney was altered. A short time ago Dr. Mott kindly discussed with me 300 necropsies in his Department, in which he had noted that if, as it commonly happened, in cases of atheroma, including the cerebral arteries themselves, the renal fibrosis was not that of granular kidney, cerebral haemorrhage was relatively infrequent. This result of a large comparison agrees with the impressions which on this subject I received when I was a Commissioner in Lunacy. Now, as Dr. Mott himself observed, in pauper asylums, there is some selection of cases; among the insane a very large proportion of the cases of arterial disease are not those associated with explosive arterial pressures and large cardiac hypertrophy, whether of renal or non-renal origin; but are of a degenerative nature, with cerebral softening in the atheromatous areas. On the other hand, it is now ascertained that in the specific disease named, well or ill, Granular Kidney, the arterial lesion begins in the kidney, and that a more extensive arterio-sclerosis does not manifest itself until in one area after another it comes about, especially in the splenic, pancreatic, cardiac, and cerebral vascular areas. Yet it seems improbable that, as under the renal disorder pressures begin to increase, the strain would tell first on these smaller visceral twigs. In the renal area, indeed, where the vasa afferentia branch off from the interlobular, the pressure gradient is falling, and in the tufts which are affected early and severely, must, both by friction and by extension of bed, fall very quickly. High tension would, and does, make itself manifest sooner or later in the aorta and great vessels; but if the finer visceral twigs are among the first to be damaged, there must be some insidious humour playing on the periphery to initiate it? In one of Roth's cases, one of true "granular kidney" in a man aged 30, with blood pressures of 185-215 (death comparatively early, presumably from intercurrent causes), although the kidneys were typical, there was but little alteration of the larger vessels. Traube's notion that constriction in the renal area would suffice to enhance general pressures was erroneous; even sudden ligation of

both renal arteries does not do it. If a peripheral arterio-sclerosis became almost universal, it is possible that pressures might rise; but in Granular Kidney such extensions come about later; while, conversely, at the outset of granular kidney, even in thirty to forty days, arterial stresses may have reached very high degrees. Certainly the high pressure is not engendered, as some have supposed, of mere chronicity.

Weigert²⁰ adopts the opinion, and it is one to which my own had independently inclined, that the secret of pressure increase lies in destruction of the renal parenchyma; Dr. Batty Shaw's conjecture also, to which I have alluded, may not be widely different. But Ziegler²¹ regards glomerular lesion as the essential factor of pressure, and thinks that, if the vessels were clear, the impaired epithelium should recover itself. Ziegler's views command attention, but to me are inconclusive because he does not always discriminate between the granular, the arterio-sclerotic, and—what is not quite the same thing—the senile atrophic kidney, two forms in which the glomeruli seem to suffer passively; a remarkable inconsistency, as he was, so far as I know, the first pathologist to recognize the arterio-sclerotic kidney: a "renal arterio-sclerotic atrophy" . . . "a special form of contraction of the organ" due primarily to sclerosis of the renal arteries with, usually but not necessarily, participation of the intimate renal ramifications also. In granular kidney, although it is true that lesion of the finer arteries of the organs is an obligate condition, as if these vessels might be the gate of entry of some histolytic substance or be peculiarly susceptible to it, we seem to have to do with some pernicious agent corroding unit by unit the whole gland.

After what has been said, we shall not wonder that lesion of the glomeruli has loomed large in this inquiry. As angry spots these structures have caught the eye of all observers, both as centres of arterial disease with quasi-infarctive effects, and of fibrous hyperplasia; lesions which, however, do not, as Jores admits, by any means always run parallel. In the arterio-sclerotic kidney also, by which I mean the state in which this organ, in association with many or most of the other parts of the body, shrinks under a general vascular fibrosis or starvation, the glomeruli seem to fail in numbers so considerable that it is not easy to say that the sum of their defect is behind that in Red Granular kidney, in which their suppression is far from being universal. Differential counts would be so troublesome that the personal equation would enter for too much; but most recent observers—Jores, for example—find no parallel between heart enlargement and suppression of glomeruli. As, however, Loeb²² assumes the rise of pressures and the growth of the left ventricle to be in direct proportion to the destruction of the glomeruli, to test this statement Jores injected a number of shrunken kidneys, but in many of those unattended with cardiac hypertrophy found the glomerular destruction to be no less; and many damaged glomeruli, whatever their remnant of functional value, were still permeable. It is a notable point in Rautenberg's experiments, to be mentioned presently, that although rise of pressure and cardiac hypertrophy supervened, the glomeruli were intact. Loeb is of course well aware that in many cases of high pressure mere obliterations in the renal area are far too limited to influence general blood pressure, while in other cases of cardio-arterial pressure strain no evidence of renal disease can be demonstrated on necropsy; wherefore he postulated some wider reflexes, operating especially through the brain—an argument in which he became speculative, if not vague. However, the point which I now desire to emphasize is that this distinguished pathologist admits the not infrequent occurrence of high-pressure cases without renal disease. Pässler is of the opinion, already mentioned, that the correspondence with the cardiac enlargement lies not merely in the glomerular but in the total renal defect, and Professor Rose Bradford seems to take a similar view. Charcot, however, argued that glomerular defect entails defect of the whole secretory unit. From Rautenberg's experiments, as in some cases of "surgical kidney," it would seem that a mere annulling of renal substance without active glomerular disease may, if large enough, provoke a rise of arterial pressures. Histologically, were the glomeruli in Bright's disease the seat not of arterio-sclerosis but of endarteritis obliterans, we might have a criterion of an irritative against an atrophic

*I take this as accepted; but I may add that Jores in his last (*D. Arch.*, 1909) paper carefully recorded the cardiac condition on Müller's method in unsorted cases of shrunken kidney and found definite hypertrophy by no means constant.

lesion of these elements. But we must take it for the present from Jores that the arterial change is arterio-sclerotic, as recognized in subintimal hyperplasia with split elastica, and in its disposition to fatty degeneration, a kind of decay to which endarteritis obliterans is less prone.

Dr. Batty Shaw³⁰ attributes the rise of pressure to suppression of kidney substance, but not in a negative sense. He looks to a positive effect of absorption of the gland into the system as a hypertensive poison; a curious construing of Johnson's presumption that the "stopcock action" of the peripheral vessels served to protect the periphery from a previously tainted blood. Dr. Shaw's conjecture is that kidney stuff of its own nature acts hypertensively; and that not in Bright's disease only but also in the hyperpietic disease of Huchard and myself the kidneys are undergoing some kind of solution and diffusion into the blood current, with the effect of general arterial constriction and consecutively of arterio-sclerosis. He supposes the only differences of Hyperpiesis to be that this solution and diffusion is not so concentrated, or so virulent, or perhaps not so specific, as to issue in the symptoms we recognize clinically as Bright's disease with its more familiar train of symptoms. Dr. Shaw alleges that injection of extract of renal cortex, prepared by the method of Tigerstedt and Bergman, drives up blood pressures to degrees unapproached by any other such organic extracts except the pituitary. However, later experiments on the point fail to support this allegation; they are doubtful or contradictory. Maragliano³⁴ made two series of experiments in this way; he injected kidney pulp of dogs into rabbits, producing—so I gather from the extracts—little rise of pressures, but a general cytotoxicity, in which the kidney was implicated. But these injections from one species into another seem open to the objection of violation of the idiosyncrasies of animal species (Nuttall and others). Pearce³⁵ injected extract of kidney—both from healthy and nephritic organs—into animals, with indecisive results; but, on the whole, so far as any effect on arterial pressures was perceptible, it was slight and transient, and followed by a fall. Also he injected serum from dogs in which large portions of the kidneys had been excised, and from others in which an artificial nephritis had been induced; but the evidence of a pressor substance, if any, was very slight. In our laboratories the researches of Professor Dixon and his colleagues and pupils have led us to similar conclusions.

However, if with Dr. Shaw we might assume a latent renal distemper sufficient to taint the blood but not gross enough to amount to Bright's disease, we might find a solution of the problem of Hyperpiesis. Dr. Shaw does not forget that renal cortex is not inexhaustible, and that under the morbid conditions postulated its reproduction could scarcely be very ready; indeed, with organs thus labile, it would presumably at no great interval of time be expended, and before that period rather reduced than multiplied. Now, the course of Hyperpiesis, as described by Huchard and myself—a disease which Dr. Shaw would draw into the net of primary renal causation—may, and frequently does, continue for years upon years—from ten to fifteen years—before its final events, not of uraemia, but of cardiac defeat or of cerebral haemorrhage, appear. And I think Dr. Shaw does not give weight enough to the experience that our cases of hyperpiesis, if detected in good time, are curable, and curable repeatedly; unless perchance he supposes that our remedies act favourably by virtue of some influence on the kidneys not directly intended or recognized by us. Again, ought we not to find that other kinds of disturbance of a kidney—as by a calculus or by a mass of tubercle, for instance—by vexing the renal tissue and by promoting the assumed disintegration of the cortex and diffusing it into the blood, should run up arterial pressures? Yet, as a rule, such incidental lesions, however solvent they may be of renal tissue around them, do not raise pressure nor deform the arteries or heart. And after all, were Dr. Batty Shaw's hypothesis to prove true, it would not set aside the practical distinctions between the series of clinical events long familiar to physicians under the name of "Granular Kidney" and the different series distinguished by Huchard and by myself as Presclerosis or Hyperpiesis.

But before dismissing mere obliteration of renal

substance as a direct cause of rise of arterial pressure, certain experiments of Rautenberg must be mentioned.²⁶ Rautenberg works in Lichtheim's laboratory at Königsberg, and his report of two long series of experiments indicates that he is an expert investigator. At first he lost many animals (rabbits), but as he became more dexterous and more successful, about half of them survived. The improved operation consisted in tying the left ureter for three weeks, a period determined by experience. Then connexion was made anew with the bladder, and the right kidney was extirpated. Some lived for nine months, two for a year and a quarter, one for a year and a half, one for a year and three-quarters, one for two years and a half. The blood pressures were found to have risen distinctly in about nine months, and were then systematically measured in them and in controls. The rise proved to be proportionate to the duration; in the longer survivors it would rise (from 110–122) to 160–170. On necropsy arterial disease was found in all these cases. The heart was in like degrees enlarged up to 2 or 3 grams; but as in these animals the organs are inconstant in size, well-marked enlargements only were accepted. As in Dr. Harvey's experiments in our own laboratories,²⁷ the arterial disease could not be called arterio-sclerosis, but a calcifying necrosis rather. Indeed, the intima of a rabbit's aorta is so thin, consisting of scarcely more than an epithelial layer, that a reactive arterio-sclerosis could scarcely be developed in it. That the rise of pressures could not have been due to the arterial disease was evident in those animals which died in the earlier stages of high pressure, when the lesions of the vessels had not advanced beyond pinpoint and pinhead spots, a stage at which they could not have had any effect on the blood pressure. Rautenberg admits that if the arterial damage be a direct consequence of rising pressures, yet some forerunning toxic condition may make the arteries more susceptible to this abnormal stress.* Harvey's researches, however, by experiments in which compression only was used, demonstrated that mechanical stress was amply sufficient to establish this arterial lesion; and Rautenberg thinks that, in the animals under his operation, mechanical stress was, at any rate, the chief cause. But in Granular Kidney, so far as the peripheral visceral arterioles are concerned, we have seen that excessive stresses could not account for their primary arterio-sclerosis. Another remarkable result of Rautenberg's experiments was that even before the lapse of nine months—before, that is, any static effects of high pressures could be determined—the serum of these animals, even to dilutions of 1 in 20, dilated the pupil of the enucleated frog's eye (Ehrmann's reaction), thus indicating that this serum contained a pressor substance.† It is possible that by Rautenberg's method the kidneys were not merely suppressed but were irritated, and so made to discharge a hypothetical "renin" into the blood; still, on the whole they point to renal negation rather than to renal poison as the cause of accumulation of pressor influences in the blood. It is to be hoped that steps will be taken to verify Rautenberg's experiments.

Now, if there be but one pressor substance concerned, either this must accumulate always by fault of the kidney or there must be alternative conditions to give rise to its formation or excess. The kidney is supposed to be not an elaborating, but an eliminating organ. Unless it is, as according to Dr. Batty Shaw, by sacrifice of its own body, it may fail to remove, but it cannot manufacture a pressor or any other poison. A failure to eliminate may, it is true, depend sometimes on transitory disorder, sometimes on incurable disease; or possibly the strain of excreting such a poison might drive the kidney into disease, though, at any rate at first, or in milder cases, one would look rather for a hypertrophy, a state, however, of which, in these circumstances, we have no experience. In the light of recent researches—on gout, for instance—the fault seems to lie not in a failure of the kidney to excrete normal waste, but of the antecedent reductive processes to render the waste into substances attractive to it. For while

* It is remarkable that even in this process of experimental abolition of renal structure by a uniformly acting cause, after death a focal distribution of the lesions was noted.

† In this connexion I would refer the reader to various interesting researches on "Sympathomimetic Amines"—for example, to Barger and Dale, Wellcome Physiological Research Laboratories (recent, but no date on reprint (1910 ?)). It is said, however, that normal blood gives more or less of Ehrmann's reaction.

refusing the gouty ingredient, they are often doing active work with other materials.

The opinion of observers who have worked at this subject is on the whole strongly in favour of some poison, whether a crude katabolic or an alien ingredient, at the back of both granular kidney and of the correlated peripheral arterio-sclerosis; these being concurrent effects of the hypothetical agent, as in the case of the similar and perhaps identical plumbous kidney. But the general arterio-sclerosis, after a while established in the large vessels, is probably less the result of poison than of consequential strain. As I have argued in respect of the kidney, so the arteries likewise by their peculiar limitations are disabled from expressing variously the various influences falling upon them; arterio-sclerosis may be their monotonous response to sundry kinds of bane. Dixon and Harvey are disposed to identify this toxic agent with a certain product of putrid meat, allied to, or even identical with, ergot; this putrid matter, formed in certain circumstances in the intestines, may be absorbed into the system to raise pressures by vaso-constriction, and perhaps also to injure the kidney directly. Abelous and Bain have reported in the urine of normal adults pressor substances which, when retained in the system, incite rises of pressure; and, moreover, may damage the kidneys. Crofton²⁸ found that certain xanthine bodies, if pressed in full doses, caused at first granular and fatty deterioration of the renal epithelium; and in animals which survived six months the blood pressures rose and intertubular proliferation of the connective elements ensued. Professor Walker Hall has made experiments of a similar kind and with similar results (see his *Purin Bodies*, 1903). But these problems are as yet very obscure and difficult. For instance, Dixon and Harvey have to evaporate a litre of urine to obtain their putrescent toxin in appreciable quantity. Meanwhile, we shall not forget Professor Schäfer's caution that in any animal dying slowly the blood may be toxic.

Renal Infections.

Let us now turn to note the effects of toxins of other and more familiar kinds; in particular, those of the infective diseases—of scarlet fever, of diphtheria, and so forth. The focal distribution of lesion might lead us to postulate that these distempers affected the renal meshes rather by bacteria than by toxins, were it not that we have seen how the simplest lesions in the kidneys may be thus partial. And, as Ribbert observes, the general trend of evidence is that in the various renal diseases toxins seem to play a much larger part than the bacteria. However this may be, the lesions of the infective diseases do tend to attack the renal epithelium, as if directly by an acute degenerative process; but—as in the puerperal kidney—this corroding necrobiosis associates itself with irritative overgrowth of the connective elements, so that an interstitial nephritis arises not distinctively glomerular in distribution. Grancher and Sargent,²⁹ in cases of toxic nephritis, noted the epithelial (and glomerular) seat of the disease and the secondary nature of the interstitial changes. The original lesion, they observed, was in the secreting epithelium, the cells of which, if not destroyed, were swollen and fattily degenerated. Many tubules had vanished; others were shrunken or moniliform; others, again, thickened and abraded. Such lesions Welsh and Flexner demonstrated in diphtheria also, and opined that they might be due to bacilli plus their soluble products, or to the toxic principle alone; or, again, that a mixed infection might occur, the diphtheria bacillus or toxin combining, for example, with a streptococcus, for multiple mischief. To add to our perplexity, the putrescent toxin of Dixon and Harvey, although a hypertensive poison, is correlated, not with granular kidney, but with a tubular nephritis and dropsy of the tissues, strikingly manifested in dropsical distension of the glomerular cavities. Toxins apart, if the renal artery be tied (in animals), the epithelium begins at once to degenerate—a degradation due, it would seem, simply to deprivation of oxygen; if the animal survives for at least six months, an atrophic fibrous, but not a "granular kidney" proper, is established. In practice we are well aware that we cannot keep too vigilant a guard over the integrity of the renal epithelium, as evidenced by integrity of its own and the cardio-arterial functions. For many months after apparent convales-

cence this vigilance, if less incessant, should at due intervals be no less searching. Now in these infective renal diseases, as may be well discerned in young subjects, the arteries are not necessarily affected (see Jores's first paper, Cases xv, xvi, xvii, xviii, both chronic and acute); not even in the scarlet fever kidney, as demonstrated in his case of the child aged 5, in which, nevertheless, the heart was somewhat hypertrophied and dilated. Riegel³⁰ has demonstrated the same rise of arterial pressure without any renal arterio-sclerosis in the scarlatinal kidney; and so has Kalt³¹ likewise. This is very puzzling. Such cases as these mark off the toxin of infective nephritis, without intimate renal arterio-sclerosis although making for cardio-arterial strain, from the poison—if such there be—lying behind granular kidney, in which the intimate renal arterio-sclerosis and the enormous cardio-arterial strain are essential, and in some way correlated, events. Heineke published a case of acute dropsical nephritis in a man aged 29, without visceral arterio-sclerosis—for example, normal spleen, pancreas, etc., as determined after death—in which, on the lapse of ten or twelve months, arterio-sclerosis appeared in the arteries of the extremities; tempting us to guess that the dropsical fluid itself might have contained an arterial poison.

Nervous Factors.

Hitherto I have said little of any nervous factor in these problems; they are baffling enough as it is, and one is unwilling to seek the obscure by way of the obscurer. Briefly, Professor Rose Bradford³² has pointed out how stimulation of many afferent nerves produces general constriction of visceral blood vessels, including those of the kidney, with consequent rise of arterial pressure; and that other great fluctuations in the renal circulation are produced by excitation of the central ends of the depressors, or, again, of the central ends of the posterior roots of certain lower dorsal and upper lumbar segments, whereby the often assumed association of renal engorgement with general vaso-constriction is manifestly obtained. But as yet from this side of the problem we receive little light, although we may speculate whether our hypothetical toxin or toxins raise arterial pressures directly by acting on the peripheral neuro-muscular machinery, or indirectly by the middle term of some renal product having such an operation? Of this at least we may be sure, that the intimate renal arterio-sclerosis of granular kidney is no incidental effect of vasomotor tides; that this primary and essential effect is brought about by some virus, whether, renally speaking, autogenous or exotic.

The Adrenals.

I must not omit to allude to Wiesel and Schur's hypothesis, favoured by Josué, that the rise of pressures in renal diseases is not attributable to the kidney at all, but is an accidental event due to a variable implication of the contiguous adrenals (the chromaffin system). The constancy of pressure excess in Granular Kidney might be explained by a special proclivity of this mode of nephritis to propagate itself in their direction; or again by some community of miscarriage in the organs as pairs. This hypothesis has called forth a multitude of papers beyond quotation; fortunately the matter is provisionally summed up for us by Erwin Thomas, of Marchand's laboratory.³³ After a close survey of a large number of specimens, Thomas concludes that in renal disease the adrenal cortex is much oftener affected than the medulla; for instance, he found in forty cases of shrunken kidney an enlarged cortex. But he often found the same enlargement where the kidneys were intact; or with simple non-renal athero-sclerosis. The medulla he found no more affected in chronic renal diseases than in relatively normal controls. In a word, he was unable to discover that either cortex or medulla behaved in ways consistent with any known morbid series, renal, cardio-arterial or other.

CONCLUSION.

In conclusion, what issues out of this discussion to elucidate the relations between arterio-sclerosis and the kidney?

May we not go this far?—That arterio-sclerosis being almost the only terms in which an artery, apart from implication in surrounding tissues, can respond to irritation, we should expect it to give this peculiar response to

various untoward influences. In granular kidney it responds first by athero-sclerosis of its intimate inter-visceral twigs; secondly, at a later period, when not these vessels but the systemic trunks suffer under another influence, under the stress, that is, of excessive pressures, the vessels again make the only response of which they are capable; they express their reaction to a different injury also in similar terms of arterio-sclerosis. Leaving now kidney disease and turning to the series which Huchard called "Presclerosis"—my Hyperpiesis—a series in which as yet the kidneys have not been convicted of complicity, we may find again arterio-sclerosis; but only after the mode which in Granular Kidney affects the arteries of large and middle magnitudes under tensile strain, a secondary, and often preventable result. To the arterio-sclerosis of Hyperpiesis the kidneys, so far as yet known, stand in no correlative relation.

But there is yet another arterio-sclerosis, or, at any rate, an arterio-sclerosis found in quite another category—namely, the arterio-sclerosis which in 1894 I separated as the senile or decreascent form. Whether it is histologically identical or not with the kind of which we have been speaking is as yet an open question; but clinically it is distinguishable, as it arises independently of high arterial pressures, or, at any rate, under pressures not excessive for the time of life. Now in this mode of arterio-sclerosis the kidney is often altered, perhaps always, more or less. This alteration, which, again, usually puts on the shape of a shrunken or deformed kidney, has little pathological affinity with the granular kidney which it may simulate. Besides the granular kidney which goes wrong with an intimate arterio-sclerosis of its own, there is a kidney deformed in the course of a general arterio-sclerosis not its own, and if more or less decaying in consequence of decay of its nutrient arteries, yet without any original perversion. A starved but not a corrupt kidney. This form some of us have long tried to differentiate, being disposed to see in it rather a negative state, a state more or less inadequate in regard of margin of safety, but sufficient for the smaller life of an elderly man. Dr. Sainsbury has emphasized "the marvellous residual vitalities of damaged organs." This kidney contains islands of fairly normal renal tissue sufficient for the humbler sphere of life, by which I was disposed to contrast it with the true granular kidney, which I had regarded as necrobiotic all through. But so sharp a contrast cannot quite be maintained; in the granular kidney, also, there are islands of fairly normal tissue, and the essential difference seems as yet to lie, not within the compass of the kidney, but—as we have surmised—in some poison at the back of the kidney and the arterial disorder alike. However this may be, the two kinds of kidney, often similar in aspect, at any rate superficially, are radically different in nature—a difference which, if hardly to be recognized in an effete organ, yet in the clinical series to which it belongs is, in uncomplicated cases, unmistakable. And in this distinction, as my citations have proved, I am far from standing alone.

Professor Lorrain Smith's conclusion in our joint paper was accordingly, that the arterio-sclerotic kidney is a local phase of general arterial disease, producing in the kidney just the alterations which it produces in other organs of the body—alterations which need not amount to anything very grievous, as they are compatible with many, if sore and yellow, years of life; but that granular kidney, on the other hand, is some form of progressive inflammation of the gland as such, the structures essential to its function being attacked. In this fatal disease arterio-sclerosis appears in two ways—primarily and essentially in the fine arterioles of the organ itself; secondarily and later in the systemic arteries, as the effect of strain under the excessive arterial pressures in which granular kidney is always and regularly involved. The arterio-sclerotic kidney, on the other hand, if it may arise in the later stage of strained arterial systems in Hyperpiesis, is most common in the decreascent form of arterio-sclerosis.

If I may formulate these provisional conclusions, they would be as follows:

CLASS A.—Chronic Bright's Disease.

A (i). Primary intrinsic intrarenal arterio-sclerosis not due to high pressures; in granular kidney constant; in other kinds inconstant.

A (ii). Secondary extrinsic arterio-sclerosis; later; due to high pressures.

A (iii). A few mixed cases; renal disease supervening on a general arterio-sclerosis, whether of "Hyperpiesis" or "Decrescence"; not originally Bright's disease.

CLASS B.—Not Bright's Disease.

B (i). The "arterio-sclerotic kidney"; kidney alteration secondary to general arterio-sclerosis, more frequently of the decreascent kind without high pressures.

B (ii). Less frequently, entailed by the consecutive arterio-sclerosis of "Hyperpiesis."

High pressures may be considered as (i) obligate with Granular Kidney; (ii) irregularly associated with other kinds of Bright's disease; (iii) independent of Bright's disease ("Hyperpiesis").

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ON THE INTERDEPENDENCE OF THE CIRCULATORY AND RESPIRATORY SYSTEMS.

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THE factors which contribute to a fatal issue in acute lobar pneumonia are very difficult to estimate. The infected patient is subjected to the adverse influences of a complicated series of abnormal processes, which, for the sake of convenience, may be termed chemical and mechanical. The chemical agencies probably include the disintegrating bacteria, the local products of the reaction between the micro-organisms and the host, and various other substances of abnormal quantity or quality which originate as a result of the interference of toxins with the normal metabolism in parenchymatous organs. These processes manifest themselves in well-recognized anatomical changes in the liver, the kidneys, and the cardiac muscle, and the clinical manifestations of the disease indicate a reaction on the part of the nervous system also. The degree to which the parenchymatous organs are affected depends on the amount of abnormal chemical substances present, and the affinity of these for the affected organs. The progress of the disease will be determined largely by the reaction of the bone marrow and other tissues which supply the antistances necessary to hold the noxious chemical processes in check. The issue of pneumonia, however, may be influenced by the variation in mechanical conditions incident to the disease. The pain of the pleurisy interferes with free movement of the chest wall, and an extensive consolidation, too, limits the expansion of the thoracic cavity and creates an obstruction to the pulmonary circulation. The work of the right ventricle is thus increased, and if the cardiac muscle be affected the efficiency of the organ may be seriously prejudiced.

In the case of those conditions which are classed collectively as bronchopneumonia in children, the mechanical difficulties are often very pronounced. Rapid respiration and cyanosis are common features of bronchitic affections, accompanied by rickets and atelectasis. In many of the cases the toxic effects of the pneumonia are much less serious than the physical disability under which the heart suffers in maintaining the circulation. An extensive clinical and correlated *post-mortem* experience has established this fact beyond all doubt.

Within very narrow limits the healthy heart preserves a definite shape and size, varying only with the age and weight of the individual. There occur, however, in