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INAUGURAL ADDRESS DELIVERED BEFORE THE MIDLAND MEDICAL SOCIETY, AT BIRMINGHAM, ON OCTOBER 28, 1909.

By Sir LAUDER BRUNTON, Bt., LL.D., M.D., F.R.C.P., F.R.S., Etc.

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When you first asked me to address you to-night I regarded the invitation as an honour and accepted it with pleasure. But I had hardly sent off my letter of acceptance than I began to repent of doing so, for on consideration it seemed to me that there was probably no subject in the whole of medical science in which some of you would not be better up than I, because the daily work of practice not only leaves me very little time for reading, but its pressure prevents me from making the experiments and investigations which I would like to do if I had more leisure. To address men who were better up than myself seemed to me very much like teaching my grandmother to suck eggs; but on second thoughts it occurred to me that from my seniority I am in the position of the grandmother, and that while I may not be acquainted with all the newest discoveries, my old experiences may be of use in aiding the work of younger men upon a subject regarding which much is still to be known, viz. the vascular troubles of later life. It is all the more likely that my own experiences may be useful, for I had the singular, perhaps unique, good fortune to work for about two years in the laboratories of four of the most distinguished physiologists of the last century, Brücke, du Bois Reymond, Kühne, and Ludwig. In Brücke's laboratory I worked on the Effect of Digitalis upon the Excitability of Muscle and Nerve; in that of du Bois Reymond on the Lifting Power of Muscle as affected by Digitalis. But these researches do not concern us to-night, and I propose to select only certain observations, which I think may have a practical bearing, from those which I either made myself or witnessed when working in the laboratories of these men.

Kühne's speciality was physiological chemistry, but he was a most accomplished physiologist and a man of marvellous ability. His work on Protoplasm and Contractility, which he published in 1864, is still, I think, the best book on the subject.* His researches on contractility naturally led him to the study of muscle, from which he separated myosin, and discovered that water is a powerful poison both to muscle and nerve when directly applied to them. In his lectures in the winter of 1868 he used to ask the question, "Why is it that a dog licks the spot where he has been bitten with comfort to himself, while if you pour water on a cut it causes great pain?" The reason is that the dog's saliva contains a certain proportion of salts which render it innocuous, and Kühne insisted that surgeons should follow the dog's example and use a normal saline solution instead of water to wash the tissues cut during operations. This advice was given forty-one years ago, yet I think it is only about ten years ago that surgeons began generally to follow it. A good deal of my time with him was spent on working at blood and digestion. One day when examining some blood with a spectroscope I decomposed it by means of an acid, and split up the hæmoglobin into hæmatin and globulin, the hæmoglobin spectrum disappearing. In some way or other I succeeded, on one occasion, in getting the hæmatin and globulin again to re-combine, and the hæmoglobin spectrum to return. I tried very often to repeat this experiment, and always failed. I have no doubt that many others have likewise failed and will disbelieve my statement, but I have no more doubt that I obtained a re-combination of hæmatin and globulin on that occasion, than I have of the fact that I am addressing you now, although I never addressed you before, and probably never shall do so again.

* W. Kühne, *Untersuchungen über das Protoplasma und die Contractilität.* Leipzig: W. Engelmann, 1864.

Another great part of my time was taken up with attempts to separate digestive enzymes and zymogens, especially from the pancreas, and to study the products of digestion. One day I put some minced pancreas and fibrin into a vessel at 40° C., and left it to digest during the whole night. Next morning when we tried to enter the laboratory it was almost impossible. The place was filled with the most awful stink that it is possible to conceive. I had to rush to the windows, throw them open, and rush out again until a current of fresh air had made the place bearable. No sewer gas that I have ever come near was anything like it. In the fluid that remained I found leucin and tyrosin amongst other products of albuminous decomposition by pancreatic digestion. The importance of tyrosin will become apparent afterwards when I come to consider the causes of rise of blood pressure in later life. Indol was also present, but how much of it was due to the action of the pancreas alone, and how much to the possible co-operation of bacilli in the digesting fluid I cannot tell, because I never had the courage to repeat the experiment.

Shortly before I began to work in du Bois Reymond's laboratory, Traube had been making in it his classical researches on the action of digitalis, and the kymograph which he used was still there. By its aid A. B. Meyer and I succeeded in getting distinct proof that digitalis contracted the arterioles and thus raised the blood pressure (1). But the rise that we obtained was insignificant, compared with that which Professor Rosenthal one day showed me as a consequence of injecting nicotine into the veins. The pressure in the arteries rose so high as to drive the float which rested on the mercurial column of the kymograph right out of the tube. I had never seen anything like it before, and I never saw anything like it again until Professor Schäfer and Dr. Oliver showed me the action of adrenalin, and the result of injecting this into a vein was precisely similar to what I had seen in Rosenthal's experiment with nicotine.

When I went to work with Ludwig, his new Physiological Institute was just being opened, and I was present at his first lecture in it. There were very few men working in it, and he gave me much of his time, doing many of the experiments himself, teaching me how they ought to be done, and telling me amusing stories all the time. He used to look back upon that time as the "honeymoon," or, as he termed it, the "Flitterwochen" of the new institute. He was then beginning to work on the process of perfusion, and to investigate the action of the arterioles in regulating the flow of blood through them. He set me to work on this, and I then observed not only that the arterioles had a power of contraction quite apart from the heart or nervous system (2), and that this contraction was not limited to a few vessels here and there as in the rabbit's ear, but that it occurred as a general process throughout the body (3). The contraction was sometimes so complete as to obliterate the lumen of the vessel. Moreover, the arterioles would sometimes contract in a completely peristaltic manner, just like a bit of intestine (4).* Other researches were also carried on, and especially one on the secretion of urine, by Ludwig, along with his pupil Ustimovitch (5), and I well remember the epoch-making experiment, almost exactly forty years ago, which led Ludwig to alter his theory of the secretion of urine. He and Ustimovitch had narcotised a dog and divided the spinal cord so that the blood pressure was very low indeed. They then injected urea into the veins, and found that the secretion of urine was very considerably increased although the blood pressure remained low. It was this experiment that led Ludwig to modify his original theory (6), and to hold that while the secretion of urine depended in general on the difference between the pressure in the renal arteries and that in the ureters, yet the rate of secretion depends to a certain extent on the amount of urinary matters contained in the blood (7). Owing to Ludwig's habit of publishing all his work under the name of his scholars, so that it was only recognised as his by being contained in his *Arbeiten*, this important addition which he made to his theory has been often overlooked, and it is, I think, not generally known that he modified his theory in this very important particular.

For the greater convenience of reference afterwards to the

* Since this paper was published, I have found that Lord Lister made similar observations on the frog in 1857, and observed in it, after removal of the brain and spinal cord, both complete contraction of an artery so as to obliterate its lumen, and peristaltic contraction. *Phil. Trans.*, Part II. for 1858, and *Collected Papers*, Oxford, 1909, vol. i. p. 39.

experiments, I may divide them into two classes : (A) chemical and (B) vital.

(A) Under the chemical we class the facts: First, that a protein molecule may be split up and again re-combined like hæmoglobin; second, that a protein molecule may be split up either by digestive enzymes alone, or by the combined action of these and bacteria, so as to yield peptones and amido-acids such as leucin (amido-caproic acid) and tyrosin (para-oxyphenyl-α-amido-propionic acid) (8), and substances of an unknown nature, but having a smell of the vilest kind.

(B) The vital phenomena consist: First, in the power of the arterioles to contract independently of the heart and nervous system; Secondly, the fact that such contraction may raise blood pressure greatly; Thirdly, that certain poisons will cause such contraction, and raise blood pressure; Fourthly, that while secretion of the kidneys depends, when other circumstances are equal, upon the difference between the pressure in the arteries and in the ureters (9), yet it may be influenced apart from the pressure, by the composition of the blood (10).

All these phenomena have, I believe, a close relationship to the subject of the paper, viz. vascular troubles in later life. I was led to choose this subject not only because my experiences might help to elucidate some points in it, but because the subject is one which must engage your attention day by day.

Birmingham is a city of strenuous life, and in it there are many men who are not content to work hard all day long in commerce, but who, instead of spending their leisure hours in exercise, rest, or amusement, occupy them with political work and excitement. The life is one in which what the Germans call "Sturm und Drang" are prominent elements. Such men may go on for thirty or even forty years working at high pressure, yet showing no external evidences of the effect of time upon them beyond a few wrinkles on the brow, a more hard and set look on the face, and a few grey hairs in the head or beard. They seem both to themselves and others to be capable of as much, or more work, than younger men. But one day some difficult problem comes before them, and they find they can no longer grasp details so readily, nor come to a decision so quickly and surely as before. They can no longer trust in the correctness of their judgment to the same extent, and little by little they become content rather to shirk responsibility, and throw it upon others. Then perhaps they begin to feel a little short of breath, or get palpitation on going upstairs to their office, or they may feel a little catch or pain across the sternum when they hurry. They get a transient attack or two of giddiness, or perhaps they feel faint and require a small glass of brandy to bring them round, or they begin to make little mistakes in speaking, writing, or spelling, to miss out words here and there, or to repeat themselves unnecessarily. They may feel a fulness in the head, or perhaps headache, a condition to which they have hitherto been unaccustomed, and fearing apoplexy, or heart disease, or that something is going wrong with their head, they come to consult a medical man. When I was a boy I used to hear a good deal about people dying suddenly of apoplexy, but there was never a word about heart disease. Later on, I heard a good deal more of heart disease and less of apoplexy, and I had the curiosity to look up the records of the Registrar-General in regard to this. I found that in 1838 the total deaths registered from heart disease were 3557, and from apoplexy 5630; that is to say, roughly, that the relation of apoplexy to heart disease was as three to two. In 1894 the total deaths from heart disease were 46,826, and from apoplexy 16,097; the relationship was thus completely reversed, and instead of the excess of deaths from apoplexy being the greater, the deaths from cardiac disease were now nearly three times as great as those from apoplexy (11). This difference in the Registrar-General's returns arose no doubt from increased accuracy of diagnosis, the cases which were formerly reckoned as apoplexy being now correctly assigned to disease of the heart.

When I was a student, one of the most honoured members of this Society, who is also an old and valued friend of my own, Dr. Edward Malins, and I were pathological clerks together. At that time pathology consisted almost entirely of morbid anatomy, and general pathology was unknown. The efforts of medical men were chiefly directed towards bringing into relationship the symptoms observed during life and the appearances presented in the post-mortem theatre. The results have been of the utmost value, as is evidenced by what I have just said regarding apoplexy and heart disease. At the same time, the constant observation of post-mortem appearances tended to bring about therapeutic scepticism, for the pathologist could not readily see how the conditions observed at an autopsy could be greatly influenced by medicines given during life. So much was this the case that one of our teachers would spend a whole hour in making an accurate diagnosis of the patient's case, and would then hurry off without prescribing anything whatever. His house physician would catch him and say, "What shall I give to the patient?" and his almost invariable answer was "Give a little aqua acetatis ammoniæ"—a drug which, if it did not do a great deal of good, certainly would not do very much harm.

Nor was too close attention to morbid anatomy the only cause of therapeutic scepticism. We had no exact knowledge of the action of medicines, and the reproach was only too true that physic consisted in pouring drugs of which we knew little into bodies of which we knew less. But at that time pharmacological observations were just beginning. Traube was experimenting on the action of digitalis with Ludwig's kymograph (12), and von Bezold was carrying on his wonderful researches on the action of atropine (13), but their work had not then become known in this country, and the same teacher to whom I have just referred, informed us in his lectures that digitalis was a cardiac depressant, and must be used with care whenever the heart was feeble. Just about this time a change was coming over pathology also. Instead of attending only to appearances in the dead-house, men were beginning to recognise that pathological processes were really physiological functions altered by disease, and that pharmacological actions were also healthy processes altered by the action of drugs. Thus pathology and pharmacology were really branches of physiology, and were to be studied by the same methods as it. But at that time physiology in this country was taught almost entirely by lectures, and medical men got no real grip of the subject until Burdon-Sanderson succeeded by his personal influence and by the publication of his *Handbook to the Physiological Laboratory* (14) in making physiology a practical study, in which each student was taught not merely by words, but by experiments performed either before him or done by himself. It was just about this time, too, that Crum-Brown and Fraser were engaged in their epoch-making researches on the relation between chemical constitution and physiological action (15), reseaches of which we daily see the fruits in the new synthetic remedies which are constantly being brought to our hand.

Between 1865 and 1875 medical research began to take a new direction, and to look more and more to the causes, rather than to the results of disease. A great impetus to this was given by the discovery that poisonous alkaloids were not formed, like strychnine and morphine, by the higher plants alone, but were also produced during the processes of putrefaction. In 1868 Schmiedeberg and Bergmann first separated a crystalline poison, sepsin, from putrefying substances (16), and later on Selmi (17), Mosso and Guareschi (18), Brieger (19), and many others followed up this line of research. Pasteur's wonderful work also directed the attention of medical and scientific men, all over the world, to the life-history of microbes, so that now we have learned that disease germs exercise their malevolent action in the human body, not so much by their actual presence in the blood or tissues, as by the poisons which they produce.

We have learned also that they form these poisons by means of enzymes contained within their bodies or excreted by them (20). These enzymes break up albuminous substances in the same way as the pancreas, with which I experimented in Kühne's laboratory, broke up the fibrin and produced the leucin, tyrosin, and abominable volatile substances which drove us from the room. But more than this, we have learned that enzymes normally present in one part of the animal body, and by which its functions are carried on, may produce in another part substances which may act as poisons, antidotes, or nutrients to the body. When one part of the body is deficient in action, or is over-active, the other parts suffer, and it is only when the functions of each part are carried on in proper relation to the rest of the body that health is established. One might almost have supposed that St. Paul had some sort of prevision of modern physiology, for he says: "The whole body fitly joined together, compacted by that which every joint supplieth, according to the effectual working in the measure of every part, maketh increase of the body" (21).

The first experiment with which I am acquainted in which an attempt was made to ascertain the effect of digestive enzymes injected directly into the blood was that of Senator (22), who extracted the ferments of pancreas by means of glycerine, and found that such a glycerine solution, though almost completely free from microbes, would produce a febrile condition lasting several days.

Brücke had shown that pepsin might be absorbed from the intestinal canal and excreted in the urine (23). During its passage through the body, however, pepsin could not digest the tissues because it only acts in an acid medium. The same is not the case with a ferment like that of the pancreas, because this acts in an alkaline medium. One might, therefore, expect that such a ferment, when absorbed from the intestines, would have a most injurious effect upon the tissues, and Senator's experiments show that it does produce fever. Many years ago I made a number of experiments with the juice of the papaw fruit, which was supplied to me by Sir William Thistleton-Dyer, of Kew. I found that it not only digested fibrin in the same way as trypsin does, but that it was also a powerful solvent of connective tissue. I was afraid, however, to administer it internally, because I did not know how far it might be absorbed and exert its digestive action not only in the intestines but on the tissues. We now know that enzymes as a rule do not remain in the body in an active state, but are present in the form of zymogens. To use a simile that I have already employed, an enzyme may be likened to an open knife ready to sever the molecules of matter, and a zymogen would correspond to the knife shut up within its haft, incapable of cutting until it was opened again. In 1869 Kühne mentioned in his lectures, which I attended, that the zymogens of the pancreas could be split up so as to produce active enzymes by treating the gland with weak acid for a while, and then neutralising. Until a few years ago it was supposed that in the body this splitting-up was done by nervous agencies, but recently Starling and Bayliss have discovered that the secretion of one gland will split up or activate the zymogens of another gland or organ (24). The secretion from the small intestine activates the tryptic ferment of the pancreas, and some secretions from the pancreas seem to have the power of activating ferments present in muscles. Nearly all enzymes have ant-enzymes, which, as I have said, may be regarded as the haft, while the enzyme itself is the blade, and when these two are combined they become inactive. When small doses of an active enzyme are injected into an animal repeatedly, ant-enzymes are formed, and its serum acquires the power of neutralising the enzyme. In this respect the action of enzymes is very like that of bacteria, and in all probability bacteria produce their toxins by means of enzymes. I believe the first man to discover enzymes in bacteria was Bitter (25), but, independently of him, Macfadyen and I demonstrated that not only did bacteria excrete enzymes, both diastatic and proleolytic, but they have the power of adapting the quality of these enzymes to the soil in which they grow (26), in the same way as Pavlov showed that the pancreas of a dog can adapt its enzymes to the food which the animal takes (27).

Through the medium of these ferments, bacteria can split up protein substances outside the body and form poisons, which remain virulent even after the bacteria themselves have been destroyed by heat. To such poisons the name of ptomaines has been given, and ptomaine-poisoning is now well known and recognised (28). Some microbes, such as the tetanus bacillus, have the power of forming toxins locally within the body, and these toxins are absorbed into the blood and kill by acting on the nervous system quite apart from the bacilli which have produced them. Other microbes produce toxins while they are circulating in the blood or are present in the tissues generally. Others, again, produce toxins in the intestinal canal, which are absorbed into the blood and may be excreted by the urine. When the kidneys are inefficient any excess of toxins may produce death. I had a patient with disease of the kidneys, who had lived for years on the Riviera on a restricted diet and remained perfectly well. Unfortunately, on a visit to London, he stayed with his brother and partook of a large dinner. Something or another disagreed with him. He absorbed more ptomaines than his diseased kidneys could excrete, and died within a week, his symptoms being first of all vomiting, and afterwards coma. One safeguard against the introduction of poisons from the intestine is the liver, the gatekeeper which guards the passage of substances from the intestine into the circulation. This gland has the two-fold power of either returning certain substances to the intestine, and thus preventing absorption, or of destroying the poisons altogether. Thus it will return copper, manganese, iron, and probably all heavy metals (29). It will almost completely destroy coniine, hyoscyamine, and cobra poison (30), or the toxin of diphtheria (31). It has the power of breaking up uric acid and forming urea (32), and appears to intercept bitter substances formed during digestion and to return them back with the bile to the intestine (33). This process is repeated again and again, until perhaps they accumulate to such an extent as to pass through the liver into the general circulation, and produce symptoms of poisoning such as headache (34). The bitterness of gall is proverbial, but fresh bile as obtained from a biliary fistula is not bitter at all (35). It is only when the bile has passed from the liver into the intestine and back again, several times, that the bitter substances increase to such an extent as to give to the bile its proverbially bitter taste.

The action of mercurials is even now imperfectly known. They are usually reputed to act as cholagogues, but according to Rutherford they do not really increase the secretion of bile (36). What they appear to do is to stimulate the peristaltic action of the duodenum, so that, in place of the bile being absorbed and again re-excreted, it is swept on to a lower part of the intestine, and there either changed by the digestive juices or excreted altogether, along with leucin and tyrosin (37). If this be so, mercurial purgatives do not merely remove bile, but they remove toxins from the body, and this is probably why their action in many cases is so very different from, and so very much more beneficial than, that of simple purgatives which act on the intestine alone. The formation of toxins in the intestine depends not only upon the kind of microbes present, but upon their relative proportion, and the nature of the intestinal contents upon which they act. As I have already mentioned microbes have the power of adapting the ferments which they excrete to the pabulum on which they feed, just like the pancreas of higher animals, but they cannot alter this power so quickly as the higher animals, and therefore one method of destroying bacteria in the intestine is to starve them out by rapidly changing their pabulum (38). This method is used in the diarrhœa of children by altering the child's food from rice-water or from hydro-carbons to albumin-water, which is purely nitrogenous, or to milk which contains a mixture of albuminous substances, sugar, and fat. Another method is that of Metchnikoff (39). He gives the lactic acid bacillus in sufficient quantity to overcome and destroy the other bacilli, and thus prevent them from forming toxins.

But toxins are much more readily formed from albuminous than from farinaceous, saccharine, or fatty foods, and abstinence from butcher's meat and restriction of proteins generally will very often prevent the recurrent attacks of so-called biliousness, vomiting, and headache (40), which appear to be due to the too-rapid formation of toxic matters, and their passage through the liver into the general circulation.

Another method still is to give intestinal antiseptics, so as to destroy the microbes, or to combine antiseptics with purgatives, especially with mercurials.

If the kidneys are healthy, toxins which have already been absorbed into the blood may be eliminated very quickly by the use of water, either alone or combined with diuretic salts, and it is extraordinary how much benefit many people obtain from a course at various watering-places. In some springs sulphates predominate, in others chlorides, in others sulphur, and the bases with which they may be combined, as well as their comparative proportion, vary to an extraordinary extent, but in all there is water, and great good can often be obtained by the free use of hot water without any addition.

Senator's experiments show that fever may be produced by the injection of pancreatic ferment into the blood, but this ceases in two or three days, probably from the formation of anti-tryptic substances.

The first observation on the internal secretions of glands were those of Bernard on the secretion of glycogen by the liver (41), and his successor, Brown-Séquard, directed attention to the possible internal secretion of the testis (42). But it was experiments upon the thyroid gland which really led to the general recognition of internal secretion (43). Large doses of the extract of this gland, or even of the gland itself, when injected into the circulation or into the intestinal canal, produce definite symptoms, quickened pulse, raised temperature, muscular tremor, subjective sensations of heat, nervous excitability, dilated peripheral vessels, lowered blood pressure and increased secretion of sweat (44). When the thyroid gland is hypertrophied all these symptoms are met with, and very often there is exophthalmos in addition. Extract of the supra-renal capsules has an action upon the circulation which is exactly opposite to that of the thyroid. It causes contraction of the blood vessels, and enormous rise of blood-pressure (45). But the anti-bodies for it seemed to be formed very rapidly, so that the effects of adrenalin pass off very quickly after its injection, and when administered by the mouth it appears to undergo change in the intestine or to be stopped by the liver, for its effects are comparatively slight. The active principle of the thyroid, on the contrary, is absorbed readily from the intestine, appears to undergo little or no change during absorption, and continues to act after reaching the circulation. It has been suggested that in the healthy body the blood pressure is to a certain extent maintained at a constant level by the opposed action of the secretion from the thyroid and from the supra-renal and pituitary glands, and it is well known that when the supra-renal bodies are diseased, the blood pressure begins to fall greatly (46). It is very likely that these glands have a most important action upon the blood pressure, but its maintenance is in all probability due to a highly complex action and interaction of glands, muscles, and nervous system, and that in considering its variations we must not attend to any one factor to the exclusion of the others. It has been supposed that the kidney has also an internal secretion, and this seems highly probable, for this gland has a very peculiar action upon certain substances which are perfused through it. When benzoic acid and glycocoll are added to the blood before passing through the kidney, the benzoic acid is converted in its passage into hippuric acid, but, strangely enough, when hippuric acid is added to the blood the reverse process takes place, and it is re-converted into benzoic acid in the kidney (47). Experiments with pounded kidney, or an extract of kidney substance, have not exhibited such a definite action on blood pressure as thyroid and supra-renal glands, but if crushed rabbit's kidney be injected into a dog several times he forms a substance, nephrotoxin, which is fatal to rabbits and produces in them rapidly fatal nephritis, and if injected directly into the carotid of a rabbit, it produces albuminuric retinitis (48). How far similar conditions may be produced in man by substances absorbed from the intestine or formed in diseased kidneys, or other organs in the man's own body, we do not know. This is a point for further research.

But this we do know, that (*a*) toxic substances may be introduced in food, that (*b*) they may be formed in the intestine itself, and if not stopped or destroyed by the liver (*c*) they pass into the circulation and act upon the body generally. We also know that (*d*) toxins may be formed within the body by the action of microbes, and that (*e*) toxic effects may be produced by the injection of normal digestive ferments or (*f*) of ferments separated from organs into the blood (49), or (*g*) by the over-action or (*h*) under-action of various glands in the body, destroying the balance of circulation and tissue change which is necessary to health.

At the British Medical Association in Belfast, in August last, Professor Dixon and Dr. Dale mentioned that two chemical bodies, iso-amylamine and para-hydroxy-phenyl-ethylamine had the same power as adrenalin of raising the blood pressure; but while adrenalin taken by the mouth has but little action, and its action, when injected into the blood, is very temporary, these substances act quite well when absorbed from the intestine, and have a much more prolonged effect than adrenalin upon the blood pressure (50). Now both these substances have been obtained from putrid meat, and they are also formed when a culture from human fæces is added to broth containing tyrosin (51). Now, as I mentioned in the beginning of my address, tyrosin was one of the substances which I obtained from the digestion of fibrin with pancreas in Kühne's laboratory, in which that awful smell was a by-product. It is quite clear, therefore, that certain substances, possibly these very chemicals which I have just mentioned, may be formed in the intestine, and after absorption may raise blood pressure continuously. For their formation may be more or less continuous in the intestine, and thus numerous small doses may be absorbed in constant succession, instead of a single dose as in Dr. Dale's experiment.

Now, a constant rise in blood pressure, whatever its cause may be, tends to produce a twofold effect, hypertrophy of the heart and increased resistance in the vessels (52). I have been trying very hard to find out the pathology of the thickening of vessels which tends to occur with advancing age, and I have not been able to arrive at a satisfactory conclusion. I find some pathologists are positive that it is change beginning in the internal coat (53), but there seems little doubt that sometimes an affection of the middle coat is chiefly of importance, and I am quite incompetent to decide on such pathological questions (54). I propose, therefore, to pass them by and simply to accept the fact that thickening does occur, and that in consequence the blood pressure tends to rise. Hypertrophy of the heart as a rule accompanies this rise, but how far it is secondary to the increased calls upon the heart's activity which the rise in pressure causes, and how far it is due to stimulation of the heart by toxins, I do not know. The rise in pressure has recently been shown to have the power of producing degenerative changes in the vessels, rendering them more liable to rupture (55). As the vessels become more and more altered, resistance to the flow of blood is increased, and the heart becomes more hypertrophied, until at last death occurs either from failure of the heart or from rupture of a cerebral vessel. In his text-book on General Pathology, Thoma says: "It is usually a cerebral hæmorrhage threatening life which leads to the physician being called in to the patient suffering from angiosclerosis" (56). This book was, however, published thirteen years ago, and much advance has been made since then. Thoma himself says: "In other cases there are hæmorrhages into the retina or frequently recurring hæmorrhages from the nasal mucous membrane which cause danger by their severity, profuse menstrual hæmorrhages which reveal the beginning of the disease." In addition to this, there are a number of symptoms such as those I have already mentioned, faintness, palpitation, shortness of breath, fulness in the head, headache, giddiness, transitory aphasia, indecision, and irritability. Some of these symptoms, such as transient giddiness or faintness, may depend upon commencing cardiac failure, so that the heart may miss a beat or two and the pressure fall. Frequently the giddiness has the characters of labyrinthine vertigo, coming on when the patient raises or lowers his head or turns it round quickly, so that it sometimes comes on in bed. The giddiness may be accompanied by slight deafness or noises in one or other ear. In such cases it may really be due to some disorder in the labyrinth, probably to atheroma of the vessels or some thickening of other tissues. It relieves patients greatly to learn that their symptoms are due to an affection of the ear and not of the brain. At the same time it must be remembered that such symptoms may indicate atheroma elsewhere, and one of my patients who came to me on account of definite labyrinthine vertigo died between three and four years afterwards of angina pectoris.

The shortness of breath is in all probability due to commencing degeneration of the right side of the heart (57), and this may ultimately lead to an entirely different kind of death, namely, gradual weakness, dyspnœa, and dropsy, the ordinary death, in fact, of mitral regurgitation. The transient feeling of pins and needles in some part of the body, transient weakness of a hand or leg, headache, temporary aphasia, and sometimes even an epileptiform fit, may all be due to small hæmorrhages or to spasmodic closure of one or other of the cerebral vessels. On post-mortem examination, small brown specks in the brain are by no means infrequent, and they probably indicate minute capillary hæmorrhages (58). The symptoms corresponding to them may also be very limited. I had one patient, a short, thick-set man, with very high tension. He was the head of a very large business and worked at very high pressure. He had gouty kidney and a small quantity of albumen. On one occasion he felt ill, and remained away from business for two or three days. On his return he was able to do everything rightly, with the exception that he could not fill in the number in a cheque. He was able to write the sum, to date the cheque, and to sign his name, but he could not fill in the figures. Some time afterwards he felt ill again, stayed away for two or three days, and on his return he was not quite so clear in his head as before. These little illnesses recurred with increasing frequency, until at last he became practically demented and died. Dr. Russell has pointed out the importance of spasmodic closure of some of the cerebral arteries in producing transient paralysis (59), and some years ago I showed that the pain in migraine, the aphasia, the hemiopia, and the anosmia which sometimes accompany this malady, might all be explained on the supposition that some of the intracranial vessels have so far contracted as to completely arrest the flow through them (60). I have felt this condition in the ascending frontal branch of my own temporal artery during migraine, and, as I mentioned at the beginning of my address, I observed the same thing in the arterioles of the rabbit's ear in Ludwig's laboratory, forty years ago. In cases where such symptoms appear, it is very important that we should be able to measure the blood pressure. Various instruments for doing this have been brought into fairly general use during the last few years (61). The one which I most prefer is a combined instrument. I use von Basch's aneroid, with a bulb on the wrist, when I wish to ascertain the pressure quickly and where a small degree of error is unimportant. For more accurate determinations I use a broad band round the arm, and connect the aneroid with a bulb to inflate it at the same time. This requires to be compared from time to time with a mercurial manometer, as the indications of the aneroid are apt to change. The normal pressure in middle life I find to be about 120 to 135 millimetres of mercury; above sixty it may rise to 145 or 150, though even then I find in some persons it remains at or below 130. As a rule when the tension is normal there is very little fear of either angina pectoris or apoplexy, but unfortunately there are some cases in which fatal angina may occur with a perfectly normal tension and apparently normal heart, and in fact no indication of danger. Sudden death occurred in one of my patients a few months ago in whom I had been perfectly unable to find anything wrong with the heart or vessels, although he had suffered from one or two slight attacks of anginal pain. I have no doubt that we shall be able by and by to ascertain the presence of a threatening condition in such cases, but at present, I, for one, do not know how it is to be done. Fortunately such cases are rare, and if we find the tension unduly high we may lower it at the first threatening symptoms by régime and medicine, and thus prolong life for a good many years. I have had under observation for nearly eleven years now a gentleman of seventy-six. He first consulted me for epistaxis. His tension was high, and I put him upon small doses of nitrite of soda. As soon as he took the medicine the epistaxis ceased. He thought at first that this was only *post hoc* and not *propter hoc*, but when he ceased the medicine the epistaxis again commenced. He repeated the experiment several times, until he found it really was the medicine which stopped the epistaxis, and he has continued to take it ever since, generally coming to me once a year to have the dose increased. A still safer plan would be for men over fifty-five, or even fifty, who are living a life of strain or anxiety, to have their tension taken occasionally by their medical man, so that he could watch for any rise. Whenever the rise begins, the amount of butcher meat in the diet should be lessened, and its place taken by fish or fowl, eggs and cheese, farinaceous food, and vegetables. Alcohol should be allowed only in moderate quantity, and moderation should also be enjoined in the use of tobacco, tea, and coffee. The patients should be warned of their condition, and advised to lessen strain, either mental or bodily, if possible. There is no mental strain so risky as that of a fit of anger, and yet it is precisely in such cases of high tension that the temper is apt to become very irritable, and angry outbursts may occur on very slight provocation, altogether out of proportion to the emotion displayed. In such cases I find a mixture of bromide of potassium and salicylate of soda very useful. If taken regularly it tends to quiet the temper, and if there is any special worry an extra dose soothes the nervous system.

At the same time one must remember that the health both of the vessels and the heart depends much upon the general condition, and if no exercise at all is taken the patient may suffer. It is well, then, to advise moderate exercise, short of exhaustion and without strain.

One question that is often asked me by patients is whether they may play golf or not. As a rule I think it is a very good game for them, but if the tension be very high I think it is advisable not to allow them to drive as far as they can, but to take two short swings in place of one long one, and rather make up their score in the putting. For men who have very little time to take exercise and who need it badly, I recommend a stationary cycle, a captive golf ball, a rowing-machine, or a punching-ball. Ordinary dumb-bell exercises and Swedish movements are very good, but have the disadvantage of being so monotonous that men will only go on for a few weeks with them and then gradually drop them. Of those machines that I have mentioned, the punching-ball is most amusing, but not the best for men with very high tension. For them I think the rowing-machine is best, because the movements can be regulated so that they either row slowly or quickly, and the resistance can be graduated to a nicety. Of all instruments for giving graduated movements the ergograph of Gärtner is the most exact, but its monotony is too great to allow of its general use.

In regard to medicines, there can be no doubt whatever that mercurial purgatives given twice a week or every other night, followed by a saline in the morning, have a distinct power to lower arterial tension, and they should be regularly employed. As Radziejewsky showed, mercurials clear out tyrosin from the bowel (62), and, according to Bayer and Walpole, without this substance those products of intestinal decomposition which cause a rise of blood pressure are not formed. A useful remedy is half a grain to three grains of nitrite of soda with 10 grains or more of bicarbonate of potash and 10 grains of nitrate of potash, taken in a tumbler of plain water or of purgative water on awaking every morning. During the day half a minim or more of liquor trinitrini just after every meal tends to keep the tension down. If it causes headache, 5 grains of phenazone along with it will usually prevent headache. If there is indigestion, it may be combined with rhubarb and soda with bismuth, or with nitric acid and bitters. In place of this, half a tablet or more of nitro-glycerine may be taken, or a tablet containing half a grain of nitro-erythrol three or four times a day.

Iodide of potassium, when tested pharmacologically by injection into an animal's veins, does not cause the blood pressure to fall as nitrites do, and its action is, therefore, of a different character. How iodide of potassium and iodides act we do not at present know, but there can be very little doubt that their continued administration does lower blood pressure. It is just possible that they act indirectly by stimulating some gland, such as the thyroid, whose secretion lowers the blood pressure. The thyroid gland certainly contains more iodine than any other gland in the body. The dry gland in the form of 5-grain tablets is sometimes very useful in lowering the pressure, even when there is no apparent diminution in the appearance of the thyroid. It sometimes causes symptoms of nervousness, but these may be to a great extent counteracted by the simultaneous administration of bromide of potassium.

But in attending to the vessels we must not forget the heart, and when the heart is tending to fail in front of the increased resistance it has to overcome, small doses of digitalis or strophanthus, say 2 to 5 minims of the tincture of either of those drugs combined with nux vomica or strychnine, should be given to stimulate the heart, while the simultaneous administration of nitrites or nitro-glycerine lessens the work it has got to perform. Much more might be said upon this subject, but I have already been too long, and I shall very shortly recapitulate the chief points in this paper:—

(1) Toxins may be formed in the intestine or (2) in the body itself; (3) that some toxins have the power of increasing the blood pressure, (4) and thus either directly or indirectly producing thickening of the vessels and hypertrophy of the heart; (5) that the vascular troubles of later life are, as Huchard has so powerfully argued, due to a condition of toxæmia; and (6) that in order to prevent angina pectoris, cardiac failure, or cerebral apoplexy, we ought to prevent the formation of toxins in the intestine, to (7) increase their elimination, and to (8) counteract their effect by nitrites and by iodides. By such methods of medication I believe it is possible in many cases to prolong active and valuable lives for several, perhaps for many, years.

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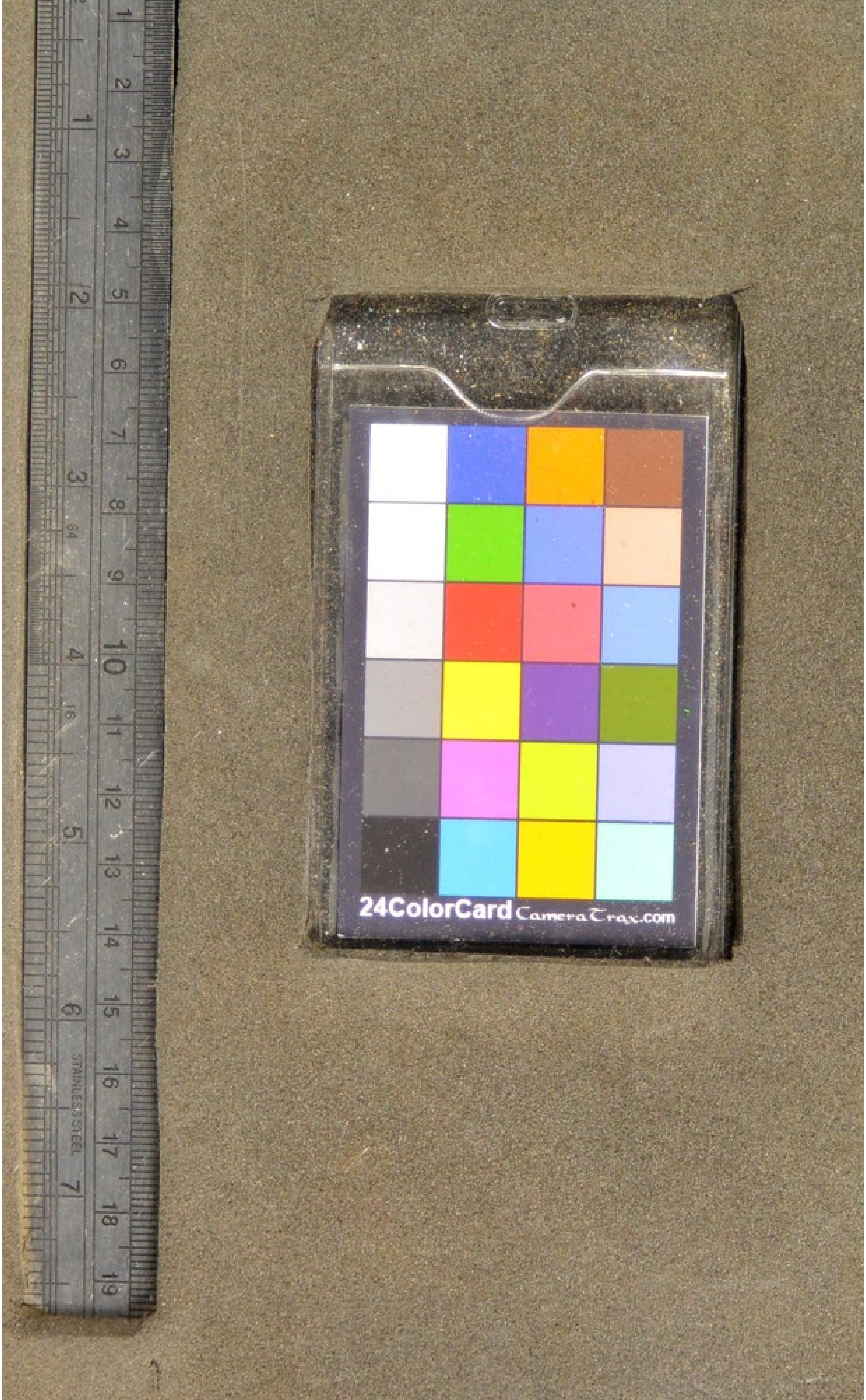
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