The Arris and Gale Lectures

ON

THE MECHANISM AND TREATMENT OF SHOCK.

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LECTURE I.—PART I.

INTRODUCTION.

MR. PRESIDENT, Fellows and Members of the College,—It is our pleasant duty cordially to thank you for the honour you have conferred upon us in electing us to deliver the Arris and Gale Lectures this year. We have chosen a subject which we believe to be of interest, not only to the operating surgeon, but also to the pathologist, physiologist, physician, and anaesthetist. We cannot lay claim adequately to represent all these branches of professional knowledge, but we have at least a sympathetic interest in them; and this research embodies a humble effort to apply physiological principles to the practical problems of medicine and surgery. Before proceeding to the lecture itself, we wish to express our deepest gratitude to our colleagues for the kindness they have shown in allowing us to take observations on their cases, often at considerable inconvenience to themselves. In particular we would acknowledge the kindness of Dr. Garrod, Dr. Batten, Mr. Waugh, Mr. Fairbank, and Mr. Pardoe. We also wish to acknowledge the assistance in taking records of Drs. Jeffries and Reynolds. Finally, we cannot adequately express our gratitude to Professors Leith and Carlier, of the University of Birmingham, for placing their laboratories and apparatus at our disposal for experimental purposes.

The problem of shock is one of the oldest in medicine, and is still certainly the most formidable obstacle to modern surgical endeavour. It is almost as old as the "everlasting hills"; certainly co-existent with the existence of man. We do not pretend to have completely solved it; rather shall we be well repaid if it is held that we have advanced in any degree the knowledge of its mechanism and rational treatment along lines which will eventually lead us to a clear understanding of its pathology and to a control of its terrors. It is, unfortunately, only too well known that in scientific research, in common with other researches, direct proof to establish the truth of any central doctrine is not always possible. If, however, we approach the subject from many different standpoints and all these lines of approach converge to meet at one point, then it is a logical assumption that that point or central doctrine is true, and the theory is as surely proved as if direct proof were possible. It is on these lines that we have studied the mechanism of shock—by an attempted combination of clinical observations, experimental and pathological research. By these we do not claim to have thoroughly exhausted or completely proved any one aspect of the problem, but rather to have attempted a comprehensive view of the subject from almost every standpoint.

We have tried to reproduce in animals some of the conditions observed by us in man, and to perform on the former identical operations, comparing the results obtained in each. Experimental work has, therefore, been approached more from the standpoint of the practical surgeon than from that of the purist in physiology. We therefore ask the indulgence of physiologists if some of our experimental methods do not appeal to them.

We entered on this research on account of the extraordinary control of shock observed in children with the

use of spinal anaesthesia; for the principle of nerve-blocking as applied in practice appeared to increase very widely surgical possibilities in those of tender years. At the commencement of our investigations we had few fixed ideas on the subject of shock, and did not possess any great knowledge of the literature. Of set purpose we refrained from consulting the views of other authors; and the fact that our observations and conclusions are made *entirely independently*, and yet so largely harmonize with some of the views of authorities on this subject, should contribute largely to their value. Again, we wish to point out that the deductions from our observations were not arrived at until from many months to one or two years had elapsed after the taking of the records. Hence the liability to error is equal for all the observations we have made; and these observations were made entirely without bias.

Since working out our own results we have studied the literature to the fullest extent we were capable of. If, therefore, in these lectures we do not often quote other authorities, or if we seem to ignore their work, it is not due to any lack of appreciation, but rather to the fact that a summary of the literature is not possible in the time at our disposal. We are fully aware of the justness of any criticism that our work has not extended over a sufficient time to warrant our conclusions. But we would state that it has occupied four years of constant labour, and we prefer at this point to give our conclusions to the profession in order that we may profit by honest criticism, and that those who are better qualified for such a task and have more time to devote to it than ourselves may take up and justify our conclusions.

METHODS OF INVESTIGATION.

Blood pressure estimations were taken at frequent intervals in a great number of surgical operations under all possible conditions of anaesthesia and anaesthetists. The difficulty of obtaining continuous blood pressure records in man, and therefore the difficulty of comparison of records in man with those obtained in animals, led us to devise a modification of Gibson's excellent instrument. A description of this instrument will appear in the forthcoming number of the *Quarterly Journal of Medicine*. By it we are enabled to record graphically the blood pressure every ten or twenty seconds for a period extending over more than two hours. Simultaneous respiratory and pulse or time tracings can be taken. The results have been plotted out on charts together with remarks as to the particular tissues being manipulated. By means of this instrument we have been enabled to compare the pressure changes in man with those in animals during the same operative manipulations, and we have learnt how valueless isolated readings of the blood pressure are in a study of surgical shock. We have examined histologically specimens in serial sections from animals we have operated on, and from the human subject, in order to ascertain what cell changes, if any, are to be noted. We are also much indebted to Dr. Rosenheim, of King's College, for his courtesy in making chemical examinations of the central nervous system in cases of clinical shock. Finally, the condition of the suprarenals in shock has been investigated, at our suggestion, by Mr. Priestley, of the University of Birmingham, in order to determine if there is any constant change in those organs in connexion with shock and conditions of low blood pressure.

RELATION OF THE BLOOD PRESSURE TO SURGICAL SHOCK.

The importance of the alterations in blood pressure to surgery are well known to all, and the many therapeutic measures for counterbalancing such effects are also well known; so that by these it is possible, to a large extent, to mitigate the injury likely to be inflicted. A study of the blood pressure under various surgical procedures has therefore in itself an important significance in the welfare of the patient, a significance to which we hope to be able to apportion its true value. But we hold that the changes in blood pressure are of vastly greater importance as a *symptom* or *sign* of infinitely graver disturbances to the physiology of the subject; that treatment to be of permanent value must be directed against the cause, however desirable it may be to relieve the symptom; and that a study of the mechanism of cardio-vascular changes resulting from surgical operations

should naturally follow the observation of such variations. Factors which normally influence the variations of blood pressure need not detain us at the present time.

Now "the whole of an animal's life may be looked upon as a series of reflex actions" (Starling), the physiological equilibrium being maintained by a succession of afferent impulses, each of which calls forth an efferent response. The most important afferent impulses which reach the vasomotor centre (Diagram I) and influence the blood

Diagram I. Impulses and routes to centres. Levels of block by different anaesthetics.

pressure are: (a) From the higher centres—for example, mental activity, emotion, etc.; (b) continuous impulses from the peripheral parts of the body. These form the most important factor to be considered in surgical operations, since it is this normal reflex which is subjected to the greatest disturbance. The study of the arterial blood pressure under these conditions, therefore, affords reliable information as to the effects of various surgical procedures on the central nervous system, provided we can appraise these variations at their true value. To do this it is necessary to eliminate the first factor mentioned, (a); further, it is essential to consider the effect of these afferent impulses on the respiratory centre, which is an important factor in the regulation of the blood pressure, and must necessarily be subject to some extent to the same influences as the vasomotor centre. The blood pressure also varies with:

1. Increased cardiac output.
2. Increase of peripheral resistance.
3. Muscular effort.

Interpretation of blood-pressure variations, therefore, during surgical operations necessitates continuous or consecutive records or tracings at short intervals of:

1. Blood pressure.
2. Pulse rate.
3. Respiration.

THE INFLUENCE OF THE HIGHER CENTRES ON THE BLOOD PRESSURE.

Diagram I is a schematic illustration of the most important influences on the vasomotor and respiratory centres which we have to consider. Regarding the vasomotor and respiratory centres as of primary importance, all impulses to these are marked as afferent by dotted lines, with the exception of those from the higher centres; efferent impulses are marked by a continuous line. A—B is the situation of the block to impulses in general anaesthesia; C—D is the situation of the block in trans-section of the cord; E—F is the situation of the block in (1) spinal anaesthesia, (2) section of the posterior roots, and (3) excision of the cord.

1. Consciousness.

Blood pressure readings were taken at short intervals on a child of about 7 years, at the Medical Society of London

(April 17th, 1910). The child was perfectly quiet and manageable. Two facts are evident from an examination of this chart. In the first place, the mean blood pressure gradually subsided as the child became mentally more reconciled to the situation. In the second place, individual variations correspondingly decrease. It seems therefore that:

The activity of the higher centres acts as a stimulus to the vasomotor centre, and this not only raises the mean level of the arterial blood pressure, but also increases the range of variations. This is further supported by tracings of a child asleep and awake; here we found that, during sleep, rapidly consecutive tracings showed that the blood pressure in sleep is about 20 mm. lower than during consciousness.

Tracings from a fretful child, during operation under spinal anaesthesia, show that these features are accentuated. In extreme mental disturbance, exemplified by a tracing under spinal anaesthesia where excitement was a predominant factor, the blood pressure is raised enormously and the variations are still more marked.

2. Consciousness of Pain.

In pain, one tracing which we have been able to obtain appears to show that the mean level of the blood pressure is hardly raised at all, but that the most marked feature is the increase in individual variations. We conclude, therefore, that the emotions raise the mean blood pressure, and increase the individual variations in proportion to their intensity, but that in consciousness of pain, perhaps the most violent of the emotions, the variations are the most distinctive feature.

INHALATION ANAESTHESIA.

Professor Crile states that "those parts of the nervous system which are embryologically and phylogenetically the oldest" . . . are the hardest and the least susceptible to inimical influences.¹ It is misleading, therefore, to state that chloroform and ether, when inhaled, paralyse from above downwards; rather must we regard a definite concentration of these drugs in the blood, as powerful enough to paralyse consciousness, which, for example, is yet insufficient to produce a similar effect on the lower centres.

(a) Chloroform Anaesthesia.

Tracings from the human subject show, as a rule, the initial rise during the preliminary excitement of the higher centres. After this the blood pressure falls proportionately to the concentration of the drug. The abolition of consciousness in chloroform anaesthesia usually induces a drop in blood pressure amounting to about 20 mm. Hg, or about the same as in the abolition of consciousness during sleep. This drop of blood pressure is attributable to the blocking of continuous impulses from the higher centres to the vasomotor centre. With regard to the respiratory centre, chloroform appears first to stimulate, then to depress, the afferent fibres which inhibit inspiration. A further concentration of chloroform appears to directly paralyse the centre itself.

It might be expected that the more resistant vasomotor centre would show signs of stimulation as the percentage of chloroform vapour increases, and that this should be indicated by a subsequent rise in blood pressure. We have never been able to detect such a rise; and it seems that, under ordinary surgical anaesthesia, chloroform narcosis within the limits of safety does not influence the vasomotor centre to any extent. Further evidence in support of this conclusion will be forthcoming. Finally, the effects of chloroform on the heart muscle itself must not be overlooked. We are led to suppose that death from "overdose" of chloroform is due, primarily, to paralysis of the respiratory centre.

(b) Ether Anaesthesia.

In the administration of ether by the open method the same preliminary rise of blood pressure is seen. When unconsciousness has been induced the blood pressure usually remains at about the same level as before induction. Individual variations, however, are much more marked. We have concluded: (1) That the fall in blood pressure, consequent on the blocking of impulses from the higher centres in unconsciousness, is compensated in ether anaesthesia by the stimulant action of the drug on the respiratory centre; (2) that the variations are

widely increased owing to the increase in the respiratory amplitude and rhythm. Finally, we cannot agree that "ether raises the blood pressure." Our observations lead us to conclude that the effect of ether is to compensate for the lowering of the blood pressure, consequent on the paralysis of the higher centres, by the stimulation of the respiratory centre and the heart; the net result being that by this mechanism the normal level of the blood pressure is approximately maintained, though with a wider range of variations above and below the mean. Further, that the concentration of this more volatile drug never reaches a degree sufficient to induce the stage of paralysis in respect of the respiratory centre.

VARIATIONS IN BLOOD PRESSURE DURING LUMBAR PUNCTURE AND THE INDUCTION OF SPINAL ANAESTHESIA.

The results of our investigations of this subject are shortly to be published in detail in the *Quarterly Journal of Medicine*. It will be sufficient, therefore, to refer briefly to the conclusions we have arrived at.

Lumbar Puncture.

The insertion of the needle into the spinal theca is accompanied by a marked elevation of the blood pressure; this is not due to the influence of pain, since it is present, though in a different degree, in unconsciousness, and even under anaesthesia. The withdrawal of cerebro-spinal fluid, and the subsidence of the emotion resulting from the puncture, are responsible for a gradual fall of pressure. But the original level is not regained within twenty minutes. We have taken tracings in various forms of intracranial pressure, and in one apparently normal subject (where the fluid was obtained for cytological examination), and we conclude that the net result of lumbar puncture is to raise the blood pressure for at least twenty minutes afterwards. The withdrawal of cerebro-spinal fluid, therefore, is clearly not responsible for the drop of blood pressure occurring about this time under spinal anaesthesia.

Spinal Anaesthesia.

Tracings show that, under dextrin-stovaine anaesthesia, a complete block to afferent impulses is instituted, and all curves are constant, independently of the nature of the operation performed. The fall in blood pressure occurring is attributable to three factors: (1) Subsidence of mental excitement after the lumbar puncture; (2) to a very small extent to muscular relaxation; (3) most of the drop of pressure observed is due to the paralysis of the thoracic, combined with supra-umbilical abdominal, muscles, and is directly proportional to the height to which paralysis is induced. Other variations observed are definitely attributable to the phenomena of mental activity, and bear no relation to the steps of the operation.

BLOOD PRESSURE VARIATIONS DUE TO AFFERENT SURGICAL STIMULI.

Any surgical operation entails the stimulation, to a greater or lesser degree, of afferent nerves supplying the operation area; these impulses we propose to study in their relation to the respiratory centre and in the efferent responses which they call forth from the vasomotor centre. Such impulses may travel by more than one route (see Diagram I): (1) They may evoke a reflex in the segment, or segments, whose afferent branch, or branches, are stimulated. It will be apparent later that blood pressure variations of this origin may, for our purposes, be neglected. (2) They may travel up to the central nervous system and evoke reflex responses according to the nature and extent of the stimulus and the condition of the centres.

Manipulations in some parts of the body will, presumably, excite more disturbance in the central nervous system than others. On what factor does the extent of such disturbance depend? Clinically we know that the degree of shock is directly proportionate to the extent of the damaged area—that is, the number of nerve fibres stimulated and the region of the body which is subjected to injury. In surgical operations we are confronted with the effects of summation of stimuli and the mechanism of the resulting fatigue or shock.

SUMMATION OF STIMULI.

Chart 21 is taken from a child during the performance of the operation of circumcision under light chloroform anaesthesia. In this chart the blood pressure and pulse-rate are both depicted.

In the first place it is noticeable that the original readings show as usual a tendency to fall: they are higher at first than is normal in a child of 3 years. The excitement stage is not shown, but, though anaesthesia is too light to depress the medullary centres to any extent, the chart shows a fall of 11 mm. Hg with the characteristic fall in pulse-rate, due to loss of consciousness.

Chart 21.—Circumcision.

The incision is made when the blood pressure stands at 106 mm. Hg; and it will be seen that during the subsequent manipulations there is a continuous and marked rise until the operation is concluded, when the reading is 146 mm. Hg (a rise of 40 mm.). After this point there is a very marked fall to 90 mm., in spite of the fact that anaesthesia is lighter. At the point x (see Chart) hot saline solution is applied to the wound, with the result that a striking rise in blood pressure to 144 mm. occurs (a rise of 56 mm.), or practically to that point which was reached under the stimulus of the operation. The nature of the stimulus to the centres, therefore, appears to have little influence on the result produced; but the extent of the excursion of the blood pressure appears to vary rather with the degree of interference (that is, intensity). Further reference to Chart 21 shows that the rise of blood pressure during the manipulations presents a "step ladder" appearance, which is suggestive of dependence on the summation of stimuli. Now, if the pulse tracing be examined, it will be seen that the variations in rapidity follow almost identically the excursions of blood pressure. The actual extent of the variations does not correspond identically in the two cases, because, in the case of the pulse, experimental error is great. Again, if, during an operation of this nature, an observer carefully examines the radial pulse, the tension will be found to increase and the percussion wave will be felt to be smaller. Further, a dicrotic pulse, such as is not infrequently observed under chloroform anaesthesia, loses this characteristic at the first stimulus of the operation.

To summarize—the stimulus of circumcision is accompanied simultaneously by: (1) A marked step-ladder rise in blood pressure; (2) a corresponding increase in pulse rate; (3) a diminution in the percussion wave; (4) an increase in respiratory rate; and (5) an increase in respiratory amplitude. Circumcision performed under spinal anaesthesia yields an absolutely uniform blood pressure line, showing: (1) That all these changes are the result of reflex response of the central nervous system to the stimulus of the operation; and (2) that this response is due to hyperactivity of all the centres influenced by the centripetal impulses.

The effects of this stimulus on the centres are therefore: (a) *The respiratory centre.* Increase in rate and amplitude tends to raise the level of the blood pressure, and to increase its respiratory variations. (b) *The vasomotor centre.* Stimulation of this centre results in efferent stimuli, passing out through the whole sympathetic system, the result being: (1) A rise in blood pressure from general vaso-constriction; (2) acceleration of the pulse-rate to a corresponding extent; and (3) a diminution in the size of the pulse, owing to the contraction of the arteries.

In order to eliminate any possibility of the variations commented on being due to other agencies (for example,

variations of anaesthesia, experimental error, etc.), we have taken charts of the same operation performed under different depths of anaesthesia. Chart 22 was taken from a boy, 2 years of age, operated on for inguinal hernia under very light chloroform anaesthesia. The respiratory and pulse rates are seen to follow the blood pressure closely, though the lightness of the anaesthesia entails a considerable variability in the readings. In spite of this, however, the respiratory amplitude (where the experimental error is very much less than in the pulse and respiratory rates) follows the blood pressure almost step for step. Here, again, the characteristic step-ladder rise, due to the summation of stimuli, is seen, and the blood pressure rises to 125 mm. Hg or 33 mm. higher than at the commencement of the operation. After traction on the peritoneum is relieved the blood pressure rapidly falls, but does not reach the level of the starting-point. In a similar operation under deeper anaesthesia the chart shows that the blood pressure variations are practically the same, but that corresponding variations in the respiratory tracing, both in rhythm and amplitude, follow the blood pressure curve to a much less extent. Now, if chloroform narcosis be induced to such a degree that the operation does not affect the respiratory tracing, it is again apparent that the blood pressure variations are in every respect similar to the preceding charts. Chart 24 represents the operation for inguinal hernia in a child of

rapidly rises, in spite of the fact that these proceedings involve a considerable amount of haemorrhage. With the attack on bony structures (the laminae) a marked alteration in the blood pressure tracing is noticed, for marked oscillations, corresponding with the repeated stimuli to bone, are evident. Each attack on bone corresponds closely with a definite "spike" in the blood pressure line, though it was not possible to indicate each separate stimulus. As the operation nears its conclusion the blood pressure continues to fall; but this fall is still occasionally interrupted by such spikes. Further study of this chart will be resumed later; in the meantime, however, we wish to call attention to Chart 26. This chart represents the operation of laminectomy on a dog, plotted out in a correspond-

Chart 26.—Laminectomy in dog (plotted out on chart like human ones).

Chart 22.

Chart 24.

Chart 25.

Three hernias for comparison. Chart 22, Light CHCl₃. Chart 24, Deep CHCl₃. Chart 25, Spinal anaesthesia.

4½ years under very deep chloroform narcosis. The respiratory lines are not charted, since they did not vary throughout. In spite of this fact, the pulse-rate and blood pressure lines exhibit precisely the same characteristics. It will be seen that the total rise of blood pressure (about 33 mm. Hg) was not affected by the depth of narcosis. Chart 25, on the other hand, shows that all these lines are practically constant when this operation is performed under spinal anaesthesia. The trivial rise at *a* is either respiratory in origin, as evidenced by the respiratory lines, which move in opposite directions at this time, or of mental origin, as shown by the pulse-trace. This chart stands in evidence that the variations we have referred to are attributable to the afferent impulses of the operation.

From these and other tracings we conclude that chloroform does not block afferent impulses arriving at the vasomotor centre unless administered in large doses over a prolonged period of time. In other words, the vasomotor centre is the most resistant of the medullary centres.

Experimental evidence supports these clinical findings. If, for instance, the operation of laminectomy be performed on a dog under chloroform anaesthesia, a definite small rise of blood pressure is observed with the skin incision. With the attack on the deep tissues the blood pressure

ing manner to the clinical charts we have already submitted. Its resemblance to those taken from the human subject is a striking feature. In the first place the rise in blood pressure at the skin incision, and the subsequent fall practically to the starting point, are again observed, and are strictly comparable with the spike accompanying the skin incision, which has been seen in the previous charts. Following this we note the step-ladder rise, consequent on the "summation of stimuli" as the stimulation of the deep tissues commences. There are two other features of interest. In the first place there is a general rise of pressure during the operation, and a fairly rapid fall as the operation nears its conclusion. The second point to which attention must be directed is the definite "spike" on the chart each time bone is attacked. It is also noteworthy that stimulation of the dura and cord by the forceps results in a well-marked rise of blood pressure. Now, the characteristic feature of stimuli produced by chipping pieces of bone is that they are short-lived; accordingly these spikes present the characters of an equal rise and fall, or approximately so—that is to say, they form a break in the step-ladder rise and fall.

It would thus seem as if the steps in the operation caused a general rise in pressure, special rises being consequent on the stimulation of specially sensitive regions,

of which bone is one. But, in comparison with Chart 26, we show Chart 27. This chart represents the blood pressure taken during the steps of a subtrochanteric osteotomy on a child. Details of the operation are given on the chart, and it will be seen that these same spikes are reproduced in Chart 27, as in Chart 26. Naturally, the perfect

motor centre in considerable detail. Ether, by its action as a stimulant both to the heart and respiratory centre, compensates for the drop in blood pressure resulting from loss of consciousness. It would be expected, therefore, that further stimulation of the vasomotor and respiratory centres, such as obtains in surgical operations, would produce

less obvious disturbances than in the case of chloroform. Experimentally, blood-pressure variations are less marked in degree when ether is employed. For experimental purposes, therefore, ether is unsuitable as an anaesthetic, for it masks the variations of blood pressure, although there is no evidence that the afferent impulses are in any way mitigated by its employment—indeed, there is evidence to the contrary.

THE RELATIONSHIP OF BLOOD PRESSURE TO THE ONSET OF CLINICAL SHOCK.

Pressor and Depressor Stages.

We must now study a case of well-marked

clinical shock, resulting from a severe operation, in order to ascertain what relation the blood-pressure changes which we have hitherto described bear to the onset of the symptoms known as shock.

The case chosen is that of a girl of 4½ years suffering from extensive tuberculous disease of the hip-joint. Mr. Arbuthnot Lane's arthrectomy was the operation performed. (The steps need not be detailed.) Chloroform was the anaesthetic administered, and ether was also given on the mask at intervals. Chart 28 represents the blood pressure throughout this operation; the respirations varied so little that they can have had practically no influence on the blood-pressure changes. The pulse-rate followed in detail the variations of the blood pressure, as in the preceding charts we have studied; it is, therefore, only charted from that point where the onset of shock was clinically apparent.

If the general character of this chart be first surveyed, it will be seen that the opening stages of the anaesthetic are accompanied by the same changes in blood pressure which have already been referred to. The skin incision, after the point *b* was followed by no rise in blood pressure, a departure from the rule in previous cases; in explanation of this it should, however, be noted that all the steps of the operation, as far as the opening of the hip-joint, were mostly through the scar tissue of previous operations. As a result, although there are fairly well-marked variations in the blood-pressure reading attributable to the manipulations of these tissues, there is no rise in the mean pressure. In fact the mean pressure from *b* to *c* shows a steady fall due to chloroform. It is only at *c*, where the joint is opened, and manipulations within its cavity commenced, that marked alterations in the blood pressure manifest themselves.

From A to B, during which time the steps of the excision and manipulation of bone are in progress, the mean curve of the blood pressure does not exhibit such a large rise as in the case of structures interference with which admittedly induces a very much smaller degree of shock (see Charts 21 to 24). The great variations or spikes in the general curve are, however, a striking feature, and these are strictly comparable with the changes already noted in operations on bone; but in the present instance these spikes are very much larger (see Chart 26).

It is significant that these large isolated rises in pressure accompany the steps of those operations which clinically are known to produce marked shock. At *b* the dislocation of the head of the femur out of the acetabulum is characterized by a striking rise of blood pressure, amounting to over 30 mm. Hg; while cutting away diseased synovial membrane *c* is accompanied by a much less marked,

Chart 27.—Subtrochanteric osteotomy (for comparison with above).

regularity of charts taken from continuous tracings in animals cannot be expected in tracings from the human subject. Nevertheless, the features observed in Chart 26 are extremely well illustrated here. Note, for instance, the general rise of a step-ladder character commencing at * and the continuation of this as the periosteum is reached at ** 1. The pause before bony manipulations are commenced is signalled by a fall in pressure after *a*. After this point the vigorous attack on bone heralds a continuation of the rise in pressure (to approximately the same level), marked, however, by special rises following the stimulation of bone by the saw. These spikes interrupt the general rise of pressure, and are of the same character as those noted in Chart 26. The cessation of bony manipulations is characterized by a fall of blood pressure at ** 2, followed by a second rise when bone is once more attacked, and yet again by a rise on wrenching the limb.

The nature of these spikes in the chart requires a moment's consideration. They may originate in one of two ways: (1) By a reflex vaso-constriction of the deep tissues in the segment or segments stimulated—that is, a local or peripheral reflex; and (2) by additional stimulus to the vasomotor centre resulting from manipulation of more sensitive structures. A study of the original tracings of the operation of laminectomy in a dog demonstrates the real central origin of these variations. Thus, with each bony stimulus, and its concomitant rise of pressure, there is an alteration in the systolic and diastolic variations. The difference between the systolic and the diastolic pressure becomes less, and the cardiac rhythm quicker, with each rise of blood pressure. Conversely, when the blood pressure falls these excursions become greater and the cardiac rhythm is slowed.

Now, the operation of cystectomy in the dog under combined spinal and general anaesthesia shows an absolutely uniform blood pressure and respiratory trace. The perfect regularity of these and of the pulse rate throughout shows that the afferent impulses to the medullary centres are completely blocked, and contrasts markedly with the tracings of a similar operation performed under chloroform anaesthesia alone. These observations demonstrate that the variations observed are the result of the afferent impulses from the operation, and are not variations due to the anaesthetic.

Operations under Ether Anaesthesia.

It has been shown that, in all probability, chloroform administered within the limits of safety exerts little influence on the vasomotor centre; further, that under the influence of this anaesthetic we are able to study the changes resulting from centripetal impulses to the vaso-

although quite definite, spike. Again, at *c*, curetting the bony surfaces of the acetabulum is characterized by another spike of 30 mm. Hg. As bony manipulations cease it is noticeable that the blood pressure rapidly drops to 86 mm. Hg (*f*). After the point *f* continuous manipulations of the soft parts and removal of bone alternate with each other in rapid succession, and, as in cases previously studied, the effects of the summation of stimuli become apparent. Thus the chart from *c* to *d* exhibits the characteristic step-ladder rise. It is again significant that each attack on bone is signalized by a spike in blood pressure up to the point *d*; and, in this respect, the features of Chart 28 up to this point are strictly comparable to those of Chart 27. At the point *e*, thirty-eight minutes from the commencement of the operation, the clinical phenomena of shock were apparent. The blood pressure at this time was 114 mm. Hg, and afterwards rose to 120 mm. Hg. It should be realized, therefore, that, at the time the symptoms of shock were first definitely noted, the blood pressure reading was, with the exception of two spikes at *b* and *c*, the highest figure reached at any time during the operation; and further, it may be emphasized that the pressure at the onset of shock stood at practically the highest sustained figure reached throughout the whole operation. The

manœuvres caused a corresponding fall of blood pressure in every instance. The cessation of all operative manipulations at *k* is signalized by an immediate and rapid rise of blood pressure (*k* to *l*). Further manipulations, *l* to *m*, repeat the phenomena already observed, though in a less marked degree; manipulation of the soft parts clearly does not compare in its effects with the attack on bone.

It should further be noted that at *l* the blood pressure is 90 mm. Hg, or about the same level as before the commencement of the operation. This level of pressure seems to have been the natural point to which the blood pressure returned when manipulations had ceased. The rest of the chart after point *m*, dealing with the effect of strychnine and atropine, is referred to later.

The interpretation of this chart must now be considered. Broadly it may be divided into two phases: (1) *A* to *D*. Here the principles evolved from the consideration of preceding charts hold good in every detail; each stimulus induced an appropriate rise in blood pressure. (2) *D* to *E*. In this phase the effects of these stimuli are exactly reversed. The truth of these observations is supported by a further reference to Chart 26. For the concluding stages of laminectomy in the dog reproduce to a large extent the phenomena seen in

Chart 28.—Excision of hip. Shock. Depressor stage, etc. (compare Chart 26).

respiratory tracing was unaffected, showing that full surgical anaesthesia was maintained throughout, and that none of the alterations in blood pressure could be ascribed to the anaesthetic. Therefore, at *e*, the activity of the vasomotor centre was at its highest. We lay stress on this fact as showing (1) that the centre is not fatigued, (2) that a low blood pressure is by no means an essential feature of surgical shock. Up to this point this chart proves that the series of pathological processes resulting from the operation, in a case which manifests clinically the symptoms of shock, are only a more advanced degree of exactly similar changes in those operations unattended by such clinical evidence.

A striking change in the character of the chart should be noted after *d*, nearly three minutes later. (During this interval bony manipulations produced the spikes shown in the chart as far as *d*.) At *g*, twenty seconds after *d*, the femoral head was dislocated further out of the joint cavity. This manœuvre caused an enormous rise of blood pressure at *b*, but, when repeated at *g*, it was accompanied by a marked fall. At *h* the saw was again applied to the femoral neck, and again this fresh stimulus is accompanied by a continued fall of blood pressure. The chart notes that these variations are not due to the anaesthetic. Again, the application of a flushing gouge (saline 110° F.) to the joint surfaces at *i* induced a fall, which was only interrupted by a very small spike. Further

this chart. We wish to call attention particularly to the fact that this reversal is an *active* process, which constitutes further evidence of the preserved activity of the vasomotor centre. If the fall in pressure were a passive one and due to paralysis of a centre from gradual exhaustion, how can the rise of pressure from *k* to *l* on the cessation of manipulations and its repeated fall on their resumption be explained? It cannot be seriously argued that the centre recovers its activity within the space of twenty seconds!

Further, a consideration of the pulse-rate over the period *d* to *e* also supports the view that these variations are active and not passive; for, were the centre paralysed, the pulse and blood pressure would no longer be under the same degree of central control. Consequently, peripheral influences would predominate and the heart would "race" against the low blood pressure and beat more slowly as the pressure rose. Reference to this chart, however, shows that the pulse-rate follows the blood pressure closely in the stage of reversal. Finally, with the swing back (passively) of the blood pressure to its intermediate position, on cessation of the stimulus, the pulse, freed from the influence of afferent stimuli, races against the low blood pressure.

STAGES OF SURGICAL SHOCK.

On these arguments we divide surgical shock into three stages: (1) The stage of stimulation, or the pressor stage;

(2) the stage of depression, or the depressor stage; (3) the stage of equilibrium, when active abnormal afferent impulses are in abeyance.

We must now consider the mechanism of this reversal.

It has been shown that every sensory nerve contains pressor and depressor fibres to the vasomotor centre; stimulation of the pressor fibres only, induces reflex vasoconstriction and cardiac acceleration, while stimulation of the depressor fibres only, induces reflex vasodilatation, and at the same time inhibits vaso-constrictor impulses. Stimulation of such a mixed sensory nerve usually induces domination of the pressor group. Domination of the depressor group only occurs (in so far as the present study is concerned) when the pressors are fatigued.

Applying these principles to the results obtained in Chart 28, we conclude the following: The first stage of shock in that operation consisted in a rise of blood pressure and an increase in the pulse-rate, consequent on the domination of the pressor impulses. At a pressor fatigue commenced. Further stimulation initiated a domination of the depressor impulses, the cessation of these impulses being marked by a passive return of the blood pressure to an intermediate level, due to the cessation of active depressor domination.

Death from Shock.

Prolongation of the stimulus during the depressor stage leads to: (1) Continuous lowering of blood pressure—this renders inadequate the blood supply to the cardiac muscle through the coronary arteries, and this fact, combined with the lack of peripheral resistance, leads to delirium cordis; and (2) anaemia and starvation of the central nervous system—if this is carried to a sufficient degree, the recovery of the centres is rendered impossible.

REFERENCE.

1 *Annals of Surgery*, 1910.

A METHOD OF ESTIMATING THE STRENGTH OF A VACCINE BY A STANDARD BACTERIAL EMULSION.

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THE following account deals with a method of counting an emulsion of bacteria of unknown strength by comparison with an emulsion of known strength—that is, a “standard”—using a differential stain (Gram’s method), and a “standard” of opposite staining properties to the bacterial emulsion whose strength we wish to estimate. Thus, if an emulsion of staphylococci has to be estimated, a Gram-negative “standard” (*B. coli*) is used, and vice versa; and by the formulae:

Gram + : Gram - :: $\times$: standard emulsion,

or

Gram - : Gram + :: $\times$: standard emulsion,

the strength is readily worked out.

The “standard” emulsion is obtained by applying the principles used in the estimation of the number of bacteria per cubic centimetre in water or sewage, and the apparatus needed is very simple, and in fact the simple forms of glassware to be mentioned shortly are much more convenient than any more elaborate. The requirements are: A well-spread twenty-four hours old agar culture of *B. coli communis*, a platinum loop, small white sterile glass beads in sterile saline, tubes of sterile normal saline, sterile test tubes, a litre measure, three or more 1 c.cm. pipettes graduated in one-tenths, a Wright’s pipette with a glass pencil mark $\frac{1}{2}$ in. from the tip, two glass-stoppered “half Winchester” bottles containing 999 c.cm. of water, three or four 6-oz. flat-sided medicine bottles containing 15 c.cm. of nutrient gelatine (12 per cent. to 15 per cent.) suitably plugged with wool and sterilized, two deep saucepans or water baths. The 1 c.cm. pipettes (rolled up in paper) and the “half Winchesters” with their contents are sterilized.

The culture of *B. coli* is now taken, and an emulsion made by pouring about 2 c.cm. of sterile saline over the agar, and then rubbing off the growth into the saline with the platinum loop. The resulting emulsion is now transferred to a sterile test tube, and some half-dozen of the sterile glass beads added.

The next step is to obtain a “convenient strength” of this emulsion to work with in the subsequent diluting experiments that are the most important part of the process. After many trials we have found that a strength roughly estimated at between 1,500 and 2,000 millions of bacteria per cubic centimetre is a “convenient strength” to use. The opacity of the emulsion which represents roughly this strength is easily obtained either by previous experience, or by allowing three to four drops of milk to mix with 5 c.cm. of water, and then diluting the emulsion from the agar down to the opacity represented by this mixture. Having diluted down the agar emulsion to this “convenient” strength, the open end of the test tube is sealed off in the flame, and the tube shaken for half an hour or more to ensure complete separation of the individual bacteria.

It is now necessary to ascertain the true strength of this “convenient emulsion.” The two water baths are next heated, one to boiling the other at 26° C., and the medicine bottles containing the gelatine put into the latter. With a graduated pipette take 1 c.cm. of the emulsion of “convenient strength” and put it into the first “half Winchester” bottle (A), stopper the bottle and shake vigorously. Place the tube containing the emulsion of “convenient strength” into the boiling water bath for a few seconds, then remove and add two drops of formalin. Take next 1 c.cm. of (A) and drop it into the second “half Winchester” bottle (B), and shake well. Use separate sterile 1 c.cm. pipettes for each bottle. From (B) with the third pipette take 1 c.cm. and carefully drop 0.5 c.cm. of this into the first medicine bottle (C), 0.25 c.cm. into the second bottle (D), and 0.1 c.cm. into the third bottle (E). Mix the contents of these bottles and lay flat on their broad side to solidify; when solid, incubate in the cool incubator. At the end of seventy-two hours rule out squares of suitable size with a grease-pencil on the bottle and count the colonies. The dilutions being known, the true strength of the “convenient emulsion” is known, an average being taken of the plates, though, as a rule, the plates come out in practically exact multiples of one another. For example, in (A) the “convenient strength” is diluted 1,000 times, and in (B) 1,000,000 times, there being already 999 c.cm. of sterile water in each “half Winchester.” Thus, if the “convenient strength” had happened to be 1,500 millions of bacteria per cubic centimetre, then 0.5 c.cm. of (B) will give 750 colonies (C), 0.25 c.cm. of (B) will show 375 colonies (D), 0.1 c.cm. of (B) 150 colonies (E).

This emulsion of 1,500 millions per cubic centimetre is now a “standard emulsion” of Gram-negative (*B. coli*) bacteria, and may be used to estimate the strength of an “unknown” Gram-positive emulsion by the following method: Having for convenience diluted the “unknown” emulsion down to approximately the opacity of the “standard” emulsion, a slide is thoroughly cleaned and passed through the flame several times to remove any traces of grease. With the Wright’s pipette equal volumes of the Gram-negative “standard” and the Gram-positive “unknown” emulsions are taken and thoroughly mixed. One end of the clean slide is slightly warmed and a portion of this mixed drop is put on this part of the slide. Using the pipette as a “spreader” a film is made, blowing across the film as it is spread. The result of the warmth and the blowing is that the film dries evenly and instantaneously. The film thus obtained is carefully fixed by passing three times through the flame, is stained by Gram’s method and counterstained by neutral red (2 per cent. aqueous). A large-sized “counting square” having been dropped into the eyepiece of the microscope, successive “squares” are counted with the one-twelfth objective, carefully noting on paper the Gram-positive and Gram-negative organisms in each “square.” When 200 to 300 of the “standard” bacterium have been counted, the total Gram-positive and Gram-negative organisms are carefully and separately added up. Knowing the strength of the “standard” emulsion the “unknown” emulsion is readily found by proportion. Thus, supposing 250 Gram-negative organisms and 200 Gram-positive organisms have been counted and the strength of