ON THE COAGULATION OF THE BLOOD IN ITS PRACTICAL ASPECTS.

*The Annual Oration to the Medical Society of London delivered
May 4th, 1891.*

By SIR JOSEPH LISTER, BART., F.R.S.,

Professor of Clinical Surgery in King's College, London.

MR. PRESIDENT AND GENTLEMEN,—Thirty years ago Dr. Alexander Schmidt, of Dorpat, enunciated a totally new view of the coagulation of the blood. Having rediscovered the fact observed many years before by Dr. Andrew Buchanan, of Glasgow,¹ that hydrocele fluid—uncoagulable in itself—is made to coagulate by the addition to it of the serum of blood already coagulated, and pursuing extended researches in the line thus indicated, he came to the conclusion that fibrin does not exist as such in solution in the plasma, but is composed of two albuminoid substances, one present in the liquor sanguinis, to which he gave the name of fibrinogen, and the other a constituent of the blood corpuscles, and this he termed the fibrinoplastic substance.²

It might be objected to Professor Schmidt that the hydrocele fluid and the various dropsical effusions with which he had worked were not fairly comparable to liquor sanguinis; that they were transudations through the walls of vessels, and that the liquor sanguinis might have become in one way or another altered in the process of transudation. This objection was, as I believe, removed by an observation made by myself about the same period.³ It had fallen to my lot to observe that in mammalia, whereas the blood usually coagulates soon after death in the heart and the main vascular trunks, in the secondary vessels it remains fluid for an indefinite period, and that not only in those of small calibre, but, if the animal be large, in large vessels also. This being understood, I proceeded as follows: Having removed a portion of the jugular vein of a horse with the blood contained in it, between two ligatures, I suspended this segment of the vein in a vertical position. In the blood of the horse, the red corpuscles behave in a totally different manner as regards their aggregation from those of a healthy man or of the ox. In the horse, instead of the red corpuscles assuming the condition of a delicate network of rouleaux, they become aggregated into dense spherical masses, often visible to the naked eye, like coarse grains of sand; and these densely aggregated corpuscles, falling more quickly than the rouleaux in the liquor sanguinis, as hailstones fall more rapidly than snow flakes, soon leave the upper part of the fluid comparatively free from corpuscles; so that within about half an hour the upper third, or it may be half, of the blood is a transparent liquid.⁴ When I had ascertained through the translucent walls of the vein that this state of things had occurred, I punctured the upper part of the vessel, so as to let out some of the clear fluid, and found that it was very slow in coagulating. In about three-quarters of an hour it had only begun to coagulate, whereas a little of this same clear fluid, to which a small portion of coagulated blood was added, clotted in a very short period. That the clear fluid did coagulate at all was sufficiently explained by microscopical examination, which showed that there were present in it some red corpuscles and numerous white corpuscles. It was obvious that if we could have separated the corpuscles absolutely from the liquor sanguinis, there would have been no coagulation at all; and as the separation of the corpuscles from the plasma had occurred, not by transudation through vascular walls but simply as the result of gravity,

it could be no longer doubted that Schmidt's conclusions were essentially right.

During the time that has since elapsed various endeavours have been made to ascertain the precise nature and mutual relations of the constituents of the liquor sanguinis and the corpuscles thus concerned in the formation of the fibrin. This inquiry cannot be said to be yet terminated, and it is, at the present time, uncertain whether Schmidt's simple original view may not be correct, that there are two albuminoid substances, one in the plasma and one in the corpuscles, which combine to constitute fibrin.

These investigations, most valuable as they are, have, as it seems to me, somewhat overshadowed the question, which is after all the most interesting to us as practitioners, namely, What are the circumstances that determine the mutual reaction of these two constituents? What are the conditions under which the corpuscles are induced to give up their element of the fibrin, to combine with the element in the liquor sanguinis? This subject engaged a large share of my attention many years ago; and, though I am afraid I have not much of novelty to communicate regarding it, yet in consequence of its very great importance, I have thought that it might perhaps be not unworthy of the circumstances in which the kindness of your Council has placed me this evening.

Shortly before my investigations began, Professor Brücke, of Vienna, had conducted an inquiry into the conditions which determine coagulation, and had arrived at conclusions which to a certain extent resembled those to which I was led.⁵ He found, as I also did, that there is a world-wide difference, in their relations towards the blood, between the walls of the living vessels and ordinary solid matter; and Brücke concluded, as Sir Astley Cooper and others had done before him, that this difference consisted in an active state of the living vessels; that the blood vessels, by an action which they exerted upon the blood, prevented it from coagulating. My investigations, on the other hand, led me to conclude that healthy blood has no spontaneous tendency to coagulate; and that the walls of the blood vessels are not active, as Brücke supposed, but passive in their relation to coagulation; that ordinary solids induce coagulation by an attractive influence—comparable, perhaps, to that which a thread exerts in causing the deposition of sugar-candy from a solution of sugar—while the healthy living tissues differ from ordinary solids in being destitute of this attractive influence.

Out of many experiments tending to this inference, published long ago,⁶ I may be permitted again to describe one which not only appears to me conclusive on the point at issue, but is also of interest otherwise. A portion of the jugular vein of an ox with the blood in it being held vertically, I cut off the upper end, taking scrupulous care that the wounded part of the vessel did not come in contact with the blood, and then passed down into the vein a tube composed of very thin glass of a calibre rather less than that of the jugular vein, its upper end being stopped by a perforated cork in which was inserted a narrow glass tube, which again was continued with a short piece of vulcanised india-rubber tubing. The tube was pressed with the utmost steadiness down into the vein, so as to disturb the blood as little as possible. In the course of time, the vein being a little squeezed, blood made its appearance in the narrow glass tube, and then at the end of the india-rubber tube. When this was the case, the india-rubber tube was secured by a clamp, and the whole apparatus was rapidly inverted, and the piece of vein withdrawn. Waterproof tissue was then tied over the open end of the large tube to prevent evaporation and exclude dust, and the tube was securely fixed and left undisturbed. Thus we had blood present in a vessel consisting entirely of ordinary solid matter, but having been subjected in a minimum degree to the influence of the ordinary solid; and the result was that when I came to examine the blood after the lapse of ten hours, I found it still fluid, with the exception of a crust of clot lining the wall of the glass vessel. This, gentlemen, seemed to me of itself to afford sufficient evidence that healthy blood has no spon-

¹ *Proceedings of the Glasgow Philosophical Society*, February 19th, 1845.

² *Archiv für Anat. Phys.*, etc., 1861 and 1862.

³ The Croonian Lecture, by the author, on the Coagulation of the Blood, *Proceedings of the Royal Society*, June 11th, 1863, p. 606.

⁴ The same thing is seen in the mixture of serum and corpuscles obtained by stirring the blood during coagulation. In that from the horse the red corpuscles subside from about the upper third of the liquid within half an hour; whereas that from the ox shows only a thin layer of serum after the lapse of twenty-four hours. I am surprised to see that in some textbooks the buffy coat is attributed to slowness of coagulation, with which it has nothing whatever to do.

⁵ *British and Foreign Medical Review*, 1857.

⁶ The Croonian Lecture, *Proceedings of the Royal Society*, loc. cit.

taneous tendency to coagulate, requiring to be kept in check by an action on the part of the walls of the living vessels. This blood had been entirely withdrawn from the vein, and yet it remained fluid except where in contact with the ordinary solid.

This conclusion has been comparatively lately strikingly confirmed by the experiments of more than one observer. I would especially allude to one performed by Professor Berry Haycraft.⁷ He has found that if a drop of blood is introduced, under suitable precautions, into a deep narrow jar of castor oil, and before the drop, which falls slowly through this oil, has reached the bottom of the vessel, the jar is inverted and the drop made to retrace its steps without having touched the glass, this process being repeated again and again, the drop of blood, having never come in contact with an ordinary solid, remains fluid for an indefinite period. This experiment may perhaps appear to some of you even more conclusive than mine, inasmuch as no coagulation whatsoever occurs in the drop of blood under these circumstances. Certainly it seems to me that it confirms in an absolutely unmistakable manner the view to which I had been previously led.

But there is also this interesting circumstance in Professor Haycraft's observation. It had been shown amply by myself that the gases of the atmosphere are incapable of inducing coagulation of the blood; but experiments like those of Professor Haycraft show that the same is the case with neutral or chemically indifferent liquids. This seems to me to be an exceedingly interesting fact, namely, that the active living tissue, such as lines the wall of a healthy vessel, in its relation to the coagulation of the blood, resembles the mobile particles of a liquid.⁸ I say the *active* living tissue, for when the living tissue becomes impaired in vital energy it behaves towards the blood like an ordinary solid. That is the case not only when a vessel is wounded, but also when it is subjected to some influence, which, without actually wounding it, is calculated to suspend or impair its vital activity. A good illustration of this is afforded by a fact which I have never before referred to, but which I have often noticed. A very valuable field for simple and instructive observations regarding the conditions that determine the coagulation of the blood was afforded by the feet of sheep, removed after the animals had been killed, the blood being retained in the vessels by a bandage applied below the part where the foot is removed by the butcher. The blood remains fluid for days in the veins of such feet, while, at the same time, the persistent vitality of the vessels is shown by the fact that they contract when exposed by reflexion of the skin.⁹ Now it happened that the butcher, in order to keep the sheep from struggling, always tied the feet together with a firm cord applied below the part where my bandage for retaining the blood was passed round; and I invariably found the blood coagulated in the superficial veins at the part where they had been pinched between the cord and the bone. There is no reason to suppose that the temporary application of the cord had deprived the veins of their vitality at the part subjected to its pressure. If the sheep had been released, I have no doubt whatever that the veins would have remained alive. But though the vessels had not been wounded, but only squeezed, only had their vital energies temporarily impaired, nevertheless the blood had coagulated in them at the part so treated. Just as by pinching a portion of the web of a frog's foot with the padded ends of a pair of dressing forceps you can induce, if you press hard enough, a degree of intense inflammatory congestion by which the pigment cells for the time being have their vital functions of diffusion and concentration of the pigment perfectly suspended, and yet are in a condition which is recoverable,¹⁰ so had these veins been subjected to an agency—the pinching by the cord—which did not actually wound

them, but merely impaired or suspended for the time being their vital power. Thus it appears that the living tissues, which, while in a healthy active state, differ from ordinary solids in not occasioning the coagulation of the blood, when lowered in their vital power, themselves act like ordinary solids, and induce coagulation.

Another point to which my investigations were at that time directed was the behaviour of the blood-clot in relation to coagulation. I came to the conclusion that an undisturbed coagulum resembles living tissue in its behaviour with regard to coagulation; that an undisturbed clot does not induce coagulation in its vicinity—a most important truth if it be such. This is well illustrated by the fact with regard to the sheep's foot, to which I have already referred. We have seen that, on the one hand, where the tight cord had pressed the veins, coagulation occurred in those veins, but on the other hand that the blood remained permanently fluid in other parts of the same vessels. In other words, the clot induced by the action of the cord upon the veins had not been able to spread, although the blood in the veins was perfectly at rest; the clot could not propagate itself. The same thing is seen in any amputated limb in which the blood vessels are sound. If such a limb is examined, say twenty-four hours after amputation, you will find that there exist clots in the vessels where they were wounded by the knife in the operation, but that elsewhere the blood remains fluid and coagulable. I came therefore to the conclusion that an undisturbed blood-clot is unable to induce coagulation in its vicinity; and I think that the instances I have given demonstrate that such is really the case.

Yet in the experiment which I have described, where a glass tube was slipped down into the jugular vein, the coagulum did propagate itself. I found, on examining such a tube ten hours after it had been charged with blood, that the crust of clot which lined the tube was only a thin one; but in another experiment, nearly two days having been allowed to pass before examination, the clot was thick, and there remained only a small channel in the middle of it, with the blood still fluid and coagulable. How is this difference of behaviour between the clot within the vessels and the clot outside them to be explained? At the time when I performed the experiment I was disposed to think that it must be due to some imperfection in the mode of performing it; that in spite of all the care that I had taken in very steadily pressing down the very thin glass tube, nevertheless the blood must have been influenced by the glass for some considerable distance.

I am now inclined to believe that another explanation must be given. It was ascertained by Schmidt that (to adopt provisionally his original nomenclature) the fibrinoplastic substance emitted by the corpuscles is greatly in excess of what is required in order to combine with the fibrinogen of the liquor sanguinis. This, in fact, is obvious from the fundamental truth that serum expressed from a shrinking clot, when added to hydrocele fluid, induces coagulation. The blood is coagulated already; the fibrin is already formed in it; and yet the serum contains fibrinoplastic substance in solution free to combine with the fibrinogen of the hydrocele fluid. Such being the case, we can readily understand that, in the experiment with the glass tube, the clot first formed, shrinking, squeezes out a little of its serum containing fibrinoplastic substance, and this, combining with the fibrinogen of the adjacent liquor sanguinis, fresh fibrin is formed, and the clot goes on perpetuating itself indefinitely, however slowly.

But how are we to explain the non-extension of the clot within the vessels in the cases referred to? how are we to explain the fact that it did not spread from the vicinity of the tight cord in the sheep's foot, and does not extend beyond the vicinity of the wound in the amputated limb? Again, why is it that the coagulum never propagates itself from the wound in the vein after phlebotomy? That wound—intentionally made somewhat gaping—is certainly, in the first instance, occupied by blood-clot. The equable flow of the venous blood does not disturb it. It is an undisturbed coagulum. But it must often happen that the clot projects more or less into the calibre of the vessel, in which case the blood, at its lee side, will lie at rest in contact with it. Yet the indefinite extension of the coagulum, which the analogy of the blood in the glass tube would lead us to

⁷ *Journal of Anatomy and Physiology*, vol. xxii, p. 582.

⁸ Dr. Freund, of Vienna, almost simultaneously and independently observed this relation of inert liquids to coagulation, *Jahresberichte für Anatomie und Physiologie*, 1886.

⁹ The blood in the amputated limb becomes gradually impaired in its coagulating property. A few hours after amputation it is found to clot more slowly than at first when exposed to the influence of ordinary solids, and after some days fails to coagulate at all.

¹⁰ See a paper by the author on the Early Stages of Inflammation, *Phil. Trans.* for 1858, Part II, p. 682.

anticipate, never occurs; and we reckon with confidence on the wound in the vein simply healing without interference with its calibre.

These remarkable differences between the behaviour of a coagulum in a glass tube and within the living vessels may, perhaps, have light thrown upon them by a fact which I have on a previous occasion brought before the attention of this Society.¹¹ I first observed it, eighteen years ago, in an attempt that I made to obtain pure blood-serum from a horse; letting blood, with antiseptic precautions, from the carotid artery into a flask that had been purified by heating it to a very high temperature. To my great astonishment I found that, although the blood of the horse coagulated as usual in the flask, the clot did not shrink in the least. Though I kept it for many days, yet there was not a drop of serum to be seen upon its surface, and the sides of the clot remained in contact with the wall of the flask. This was made particularly striking by the circumstance that masses of aggregated red corpuscles, resembling grains of sand, as before described, were to be seen touching the glass in the lower part of the buffy coat. This, I need hardly say, astonished me immensely; and I imagine it was the first time that a blood-clot was ever seen not to shrink and press out serum.

It seemed scarcely credible that this result could be due to the destruction of micro-organisms in the flask, although the heat had been applied for that purpose. It was suggested to me that perhaps it might arise from some physical change in the glass due to the very high temperature to which I had subjected it. It had been observed by Liebig that, whereas a supersaturated solution of sulphate of soda is, under ordinary circumstances, made to start into a crystalline mass by contact with a glass stirring rod, no such effect is produced by the rod if it is heated in the flame of a spirit lamp and allowed to cool: a result attributed by Liebig to some temporary physical change produced in the glass by the heat. Might it be, then, that the fibrin of the clot failed to shrink in consequence of a different molecular arrangement assumed under the influence of the glass altered by heat? That view, however, has been exploded; because it has been proved, as illustrated by some striking experiments shown at a *conversazione* of the Royal Society some years ago by my colleague, Professor Thomson, that the cause of the crystallisation of the supersaturated solution of sulphate of soda is not the contact with the glass as such, but the accidental presence on the glass of minute quantities of sulphates isomorphous with the sulphate of soda; and that the effect of the heat is to drive off the water of crystallisation of those salts, and make them no longer isomorphous with it, and, therefore, no longer able to induce the crystallisation. And so a mystery in physics was cleared away, and made a very simple matter. Thus the suggested explanation fell to the ground.

The same absence of shrinking of the clot had been brought about by different means in the example which I exhibited to this Society five years ago. A glass jar, not especially clean, had been purified by means of a solution of corrosive sublimate in 500 parts of water. Blood had been let into this jar from the jugular vein of a horse, under antiseptic precautions, forty-one days before; and the members of the Society had the opportunity of seeing that, just as in the case of the flask subjected to a high temperature, the clot had not shrunk: the serum had not been squeezed out of it. And although it seems unlikely that in the short time that elapses between the shedding of the blood and the commencement of shrinking of the clot under ordinary circumstances, the micro-organisms present could have had such an influence on the blood, yet when we see that two agencies so different in their nature as a high temperature and a solution of corrosive sublimate, but both powerfully germicidal, led to the same result, one is almost inclined to think that surely it must be so. No other explanation has been offered, although I know that physiologists have been much interested in the subject.

If we admit that micro-organisms are the cause of the shrinking of the clot, it follows that a coagulum formed within the body under healthy conditions otherwise, being free from micro-organisms, will not shrink; and, therefore, that the clot, not squeezing out the serum, will not induce coagulation in its vicinity. Fibrinoplastic substance exists, no doubt,

in the serum in the substance of the clot. But the experiments of the late Mr. Graham showed that diffusion of liquids is an exceedingly slow process, even between a strong saline solution and water; and it must be a very slow process indeed between two liquids so nearly allied as liquor sanguinis and serum. I do not say that this is really the true explanation; but it seems to harmonise with the facts.

While an undisturbed clot resembles healthy and active living tissue with respect to coagulation, an injured clot acts in this relation like wounded tissue. And as a coagulum is an exceedingly lacerable and very easily injured substance, we often see coagulation induced by a blood-clot that has been disturbed. This is perhaps most strikingly seen in aneurysm. Let us take, for instance, a traumatic aneurysm. The blood escapes from the wounded artery into the surrounding tissues; and these having been injured, the blood coagulates in contact with them. Every successive portion of blood driven in by the force of the ventricle stretches and lacerates the clot so formed. It is an injured clot, and induces coagulation in its vicinity: and the result comes to be that while, on the one hand, the force of the heart tends perpetually to distend the sac, inferior as it is in elasticity to the wall of the artery, there is on the other hand a constant tendency to deposition of fibrin upon the interior of the sac as if the blood were "whipped," and thus the wall of the sac is perpetually strengthened, exhibiting a counteracting agency tending to recovery.

A beautiful converse of this state of things is presented, as it seems to me, by some cases of varicose aneurysm, such as used to be a not uncommon result of careless venesection. Here the communication with the vein was sometimes so free that the blood driven in by the heart distended the sac comparatively little, so that the aneurysm had no tendency to increase, but was merely a source of annoyance from the purring sensation caused by the arterial blood driven into the vein. And if an operation was performed on such a case, the remarkable fact was disclosed that instead of the aneurysmal sac being lined with layers of fibrin, it resembled in its interior an artery or a vein.¹² The force of the blood not being able to tell upon the clot and injure it, the clot ceased to induce further coagulation, and became organised and invested with endothelium.

We see the same thing illustrated in the different behaviour of the blood clot above and below a ligature applied upon an artery in its continuity. When such a ligature was applied in the old-fashioned way, in the shape of a silk thread, used without any antiseptic precautions, with the ends left long, it had to come away by suppuration, and there was serious danger of secondary hæmorrhage. But if this did occur, it was commonly not, as might have been expected, from the cardiac side, where the seat of ligature was subjected to the full force of the ventricular contractions, but from the distal side, where the pressure was comparatively feeble. The ligature having been applied sufficiently tightly to rupture the internal and middle coats, there necessarily occurred as an immediate result a certain limited amount of coagulation upon the injured tissues. On the cardiac side, where the force of the blood driven by the heart against the obstruction told powerfully at every stroke, the clot was perpetually disturbed, and infallibly coagulation occurred up to the first considerable branch, that carried the stream away and made further coagulation impossible. But at the distal side, if the circumstances of the anastomosing circulation were such that there was no pulsation, there might be no extension whatever of the undisturbed primary coagulum, so that a mere trace of clot was found on pathological examination.

I have hitherto referred to the view first advanced by myself and now, I believe, generally accepted—that the fluidity of the blood is not due to active operation of the living vessels. But I am far from holding the opinion that there is no part of the vascular system that actively opposes coagulation. If transfusion is practised in the ordinary manner—say by filling a syringe with blood and injecting it into the vessels of the patient—the blood is subjected to the influence of an ordinary solid, which would inevitably induce coagulation within the vessels, unless there were some counteracting influence at work. It is astonishing how very short a period

¹¹ BRITISH MEDICAL JOURNAL, October 25th, 1884.

¹² Syme's *Principles of Surgery*, 5th edition, p. 140.

of contact with an ordinary solid determines the mutual reaction of the corpuscles and the liquor sanguinis. Yet no coagulation occurs as the result of such an operation. It is, I presume, in the capillary system that the correcting influence is exerted.

Again when intense inflammatory congestion is produced by the application of some irritant substance to the web of a frog's foot, we see that the corpuscles, both red and white, adhere to one another and to the walls of the vessels, and block the capillaries. Mechanical violence is one of the many irritating agencies which produce such congestion; and from what we know of the effects of the pressure of the cord upon the vessels of the sheep's foot, we cannot doubt that the blood must be coagulated in the congested vessels: that between the corpuscles there must be cementing fibrin. The distinguishing characteristic of acute inflammatory exudation is of itself pretty clear evidence to this effect. The exudations in intense inflammation differ from those of dropsy by being coagulable; hence the brownness of tissues that are intensely inflamed, or the lymph in acute pericarditis. How can this coagulable character of the effused liquor sanguinis be explained except by supposing that the walls of the capillaries have acted for the time being like ordinary solid matter, and that, as a consequence of this behaviour of the capillaries, the corpuscles have given up to the liquor sanguinis (to use Schmidt's language) the necessary fibrinoplastic substance? And if the exuded liquor sanguinis coagulates, we cannot doubt that the plasma which remains in the capillaries is also coagulated. Nevertheless, if the irritant has not been pushed so far as to cause the death of the part on which it has acted, the tissues in due time recover, and we see the corpuscles gradually detaching themselves from each other, to pass on into the circulation. And we may surely say that, not only do the corpuscles recover their original non-adhesive character, but the fibrin which binds them together is redissolved.

I believe, therefore, that although in the larger vessels the vascular walls are negative as regards the coagulation of the blood, in the capillary system there must be potent agencies counteracting any tendency to clotting induced by abnormal conditions, and capable even of redissolving fibrin.

A CONTRIBUTION TO THE STUDY OF CHLORALAMIDE.

By JOHN GORDON, M.D.,

Physician Aberdeen General Dispensary; Assistant to the Professor of Materia Medica, University of Aberdeen, etc.

CHLORALAMIDE was introduced by Professor von Mering, of Strassburg. The advantages claimed for it over some of the other hypnotics are that it does not depress the cardiac, respiratory, or cerebral centres, the blood pressure is not markedly lowered, and it does not interfere with the normal course of digestion. Over sulphonal, the advantages claimed are that its action is more speedy, its use is not marked by depression, giddiness, motor inco-ordination, or deferred action. Chloralamide is further free from the somewhat deterrent taste and smell of paraldehyde, and is more active than urethane.

PHYSICAL PROPERTIES AND CHEMICAL CONSTITUTION.

Chloralamide occurs in white crystals which have a slightly cool bitter taste. It is soluble in water to the extent of about 1 in 10, in alcohol it dissolves in about 1 in 1½. If dissolved in water of temperature above 120° F., it decomposes. It is also decomposed by a caustic alkali, by carbonates or bicarbonates of an alkali, but its solubility is increased and its decomposition is prevented by the presence of a weak free acid such as hydrochloric. Chloralamide is the result of the chemical combination of chloralhydrate CCl_3CHO , and formamid CHO NH_2 , or the formula may be thus expressed:

REFLEX FUNCTIONS OF THE SPINAL CORD.

Numerous experiments were performed on frogs to elucidate its action on the reflex function of the spinal cord. The

method employed was in all essential points similar to that described in my former studies. The result of these observations was to show that chloralamide diminished the reflex functions of the spinal cord. This was shown by the long delay of the period at which the limbs were moved or withdrawn from the stimulant after the injection of the drug. Chloralamide did not diminish, at any rate in any marked degree, peripheral sensation, for it was found that the non-ligatured limb continued to be more active in response to the stimulant than the ligatured limb. In this point the drug contrasts with paraldehyde, urethane, and sulphonal, all of which had distinct influence in diminishing peripheral sensation.

EXPERIMENT I.—To give an example, the following is a type. Frog, 34 grammes in weight, decerebrated, right iliac artery and vein ligatured; stimulation in H_2SO_4 (1 in 800), 5 minims 6 per cent. Chloralamide solution injected into dorsal lymph sac.

Before Administration of Chloralamide.			
Ligatured Limb.		Unligatured Limb.	
8 seconds limb withdrawn	...	7 seconds limb withdrawn	...
6 " " "	...	5 " " "	...
6 " " "	...	6 " " "	...
At 2.50 P.M., 5 minims, 6 per cent. solution chloralamide injected into dorsal lymph sac.			
Ligatured Limb.		Unligatured Limb.	
15 seconds limb withdrawn	...	18 seconds limb withdrawn	...
19 " " "	3.30 P.M.	2 " moved	...
20 " " "	3.55 P.M.	10 " withdrawn	...
20 " " "	...	8 " moved	...
...	4.15 P.M.	28 " withdrawn	...
No movement	...	20 seconds, withdrawn with difficulty	...
...	5 P.M.	20 seconds moved feebly	...
...	11 A.M. next day; H_2SO_4 (1 in 400).	30 seconds feeble movement.	...
No response...	...	30 seconds feeble movement.	...

Experiments were also performed to test its action on frogs, and these confirm the observations of Kny, published in the *Therapeutische Monatshefte*, Heft 8, 1889. It had a distinct hypnotic effect, and diminished all the reflexes, but the frog ultimately recovered.

EXPERIMENT II.—A frog of normal activity, 32 grammes in weight, was taken at 9.35 A.M.; 15 minims of 4 per cent. solution of chloralamide was injected into dorsal lymph sac. At 9.55 its leap was heavy, fore and hind limbs were weakened, reflex of eye diminished; if placed on its back it occasionally struggled to right itself. At 10.8 reflex gone, but immediately after testing a strong co-ordinate spring was made; tendency of movement to be laboured. At 10.12 high spring made, and has since lain on its back. At 10.14 it turned suddenly to its right side, and executed violent movements of flexion and extension, and regained a sitting position. At 10.17 conjunctival reflex abolished; leg remained in same position when extended; when turned on its back made efforts to rise, but failed, and remained motionless on its back, with the legs drawn up. At 10.55 no reflex of eye or hind limbs; respirations very feeble; no cardiac pulsation visible. At 2.50 P.M. no reflex present except that of eye, but it is distinct. At 3 reflexes present in fore and hind limb and eyes, but all feeble. At 5 all reflexes present, and stronger than when last noticed. At 6.10 reflexes present, still feeble, feeble jerking efforts to move head and fore limbs. At 8.30 all reflexes present stronger than last; efforts to move more marked. By the close of the succeeding day the frog gradually recovered its normal activity.

BLOOD PRESSURE AND RESPIRATION.

Kymographic experiments on blood pressure and respiration were performed. The following observations were made, showing its action on the smaller carnivora. The drug was injected into the peritoneal cavity, afterwards into the left femoral vein, and finally into the peritoneal cavity. It will be seen from the chart that there is a slight lowering of the blood pressure after the injection, but it was only when a considerable quantity was injected, so as to reach the heart almost directly, that its influence in lowering was at all marked. Its action on the pulse was, practically speaking, slight, for at the beginning of the experiment the pulse rate was 144 per minute, and after the various injections it became accelerated to from 156 to 168 per minute, while at the end of the experiment it slowed to the initial rate of 144 per minute. Its action with the smaller doses was to increase the respirations, but with larger doses there was marked slowing and weakening, and finally complete cessation. Thus before injection the respirations were from 48 to 54 per minute; after the first injection the rate was increased to from 60 to 66 per minute. After the larger injections the rate diminished to 44, 48, 34, 40, and 36 per minute, at which periods, in addition to the