Methods and Consequences of Lowering the Blood Pressure

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The Campbell Oration
delivered to the Ulster Medical Society, 28th February, 1957

ONE of the more striking changes in the climate of physiological and pharmacological opinion, both in the laboratory and in the clinical field, is the interest taken in deliberately lowering blood pressure. Ten or twenty years ago a blood pressure below 100 mm. Hg. was regarded, in general, as undesirable, and the clinician would be tempted to start vigorous therapy, for instance, by blood transfusion or sympathomimetic amines. But recently two important things have happened. On the one hand, ganglion blocking agents have proved able to benefit malignant hypertension, and to do this (it seems) in proportion to their ability to reduce the blood pressure; on the other hand, lowering the blood pressure has been found useful at surgical operation, to diminish hæmorrhage and possibly to confer other advantages. One only appreciates this change of opinion if one looks back at older papers and sees, for instance, how the argument was advanced that high blood pressure in hypertension was a *useful* compensation, ensuring a satisfactory blood supply to organs in the presence of constricted arterioles.

Not all the fruits of the change of opinion are entirely beneficial. The blood pressure is sometimes lowered too often, too far, and too long. But such hypotension is clearly not intrinsically as dangerous as it was thought to be; and to produce it, by means which are understood and controllable, places in the hands of the clinician a therapeutic weapon of the first importance. At the same time the fashion for hypotension of one sort or another leads sometimes to failure to distinguish the means by which this hypotension is brought about. Accordingly, I want to start by some quite simple remarks "comparing and contrasting" (as examination papers have it) the various means by which a reduction of systemic blood pressure can be achieved by the use of drugs. Suppose one considers the simple cardiovascular reflex arc from various afferent nerves, through the central nervous system and out by the sympathetic outflow to arteriolar smooth muscles. First there are substances like the veratrum alkaloids; these have a fairly complex action, but a part of it at least is stimulation of vagal afferent nerves in the heart and lungs (the so-called Bezold-Jarisch effect). As a consequence of the incoming volley of impulses, the central nervous system reacts by producing a marked slowing of the heart and some peripheral vasodilation. The response is abolished

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if the drug is prevented from reaching the vagal afferents, if the vagus nerves are cut, or if the central nervous system is destroyed. As a method of lowering the blood pressure it has the interesting advantage that it does not weaken the other reflexes controlling the blood pressure, so that postural hypotension does not occur. But it possesses the disadvantage that the effects of the incoming volleys on the central nervous system are not exclusively on the circulation. There is also, as with so many reflex stimulants of this type, considerable malaise, nausea, and even vomiting. It is difficult to find a dose which secures the hypotensive action wished for, without actively unpleasant side effects. This action of veratrine is shared by a number of other compounds, by heterologous serum in some animals, and perhaps by digitalis. It is an important action in principle, which may yet come to major usefulness.

A second type of action is on the central nervous system. Drugs like phenobarbitone have an honourable history for a sedative action, by which the blood pressure of a benign hypertensive may be restrained from at least the grosser fluctuations. One presumes that phenobarbitone exerts its effect by depressing the central drive on the sympathetic centres. Such a central sedative process is undoubtedly of great use in handling hypertensive patients, but it is limited by the fact that the sedative will, if given in larger doses, inevitably cloud other central activities. I am not aware of any central sedative which will produce large falls in blood pressure without producing marked central signs, or even frank anæsthesia.

Third are the drugs which interfere with the preganglionic nerves. At present these are chiefly pharmacological curiosities. The preganglionic nerves are cholinergic; and there are substances like local anæsthetics (Harvey, 1939), botulinum toxin (Burgen, et al., 1949), and a recent compound which can be regarded as or antimetabolite for acetylcholine synthesis (MacIntosh, et al., 1956), as well as changes in ionic concentration at the nerve endings (notably Ca + + lack (Harvey and MacIntosh, 1940)), all of which interfere with the nerve terminals so as to reduce the amount of acetylcholine released at the synaptic junctions in the ganglion. As a result, one obtains a block of transmission in the ganglion due to a *lack* of transmitter rather than an antagonism to the transmitter once released. But this type of action is obviously useless to practice at present; botulinum toxin poisons all cholinergic nerves so that a depression of autonomic outflow would only be obtained at the expense of widespread neuromuscular block; local anæsthetics are too weak and non-specific; and the change in calcium concentration required to produce the effect would throw any animal or patient into violent tetany. This is another attack which doubtless will bear fruit in the future.

The fourth type of action to consider is the one in which we are primarily interested, that of specific competitive ganglion block, whereby a drug like hexamethonium stops the acetylcholine still normally released, from exciting the ganglion cells in its usual way.

Fifth are the drugs which may interfere with the postganglionic neurone and its nerve endings. A few years ago one would have made simply formal acknowledgment of the possibility that an action might take place, but this is now more

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than a possibility. There is the xylyl choline ether known as TM 10 synthesised by Hey and studied by Bain and his colleagues (Bain and Fielden, 1956) which can depress adrenaline output. Miss Vogt in Edinburgh has recently shown (Muscholl and Vogt, 1957) that reserpine can also depress adrenaline output in a rather interesting way, by depleting the neurone of its stores of the transmitter, in this case noradrenaline. Thus, although the nerve is in principle undamaged, yet it cannot release its normal amounts of sympathin because its stocks have been removed by some interference with its binding or metabolic production. It is interesting too that there are signs that morphine also can interfere with the release of transmitter at the post-ganglionic level.

Sixth, we have those drugs which can antagonize a transmitter once it has been released at the peripheral site; that is to say, drugs like dihydrœrgotamine or dibenzyline at the sympathetic sites. For lowering the blood pressure, of course, the antiadrenaline drugs are of great importance, although perhaps they deserve attention chiefly for investigative purposes rather than treatment.

The last (seventh) group of actions are those where the drug concerned has a direct action on the smooth muscle of the arteriole wall, causing it to relax. Here one has in mind things such as the nitrites or acetylcholine or histamine. But they are all rather transient; and with one exception in principle, which I will discuss later, that of histamine release from the body, I am not aware yet of any particularly encouraging evidence that such drugs can be used for any length of time for lowering the blood pressure.

The Proof of Ganglion Block.

Looking at the various methods of reducing the blood pressure, ganglion block offers one significant advantage. This is that the autonomic outflow can be interrupted without, on the one hand, any action of the central nervous system (such as phenobarbitone exerts) nor, on the other hand, any action on the effector organ; the latter thus retains its sensitivity to drugs like acetylcholine or adrenaline if one wants to control an excessive degree of block. But this advantage with ganglion block only exists if the blocking agent is in fact *specific*. To illustrate what is meant by this, and to exemplify part of the work of pharmacological research, I would like briefly to review the evidence one has to collect before ganglion block can be taken as the sole action of a particular compound. The work I am going to describe was done some years ago by Dr. Zaimis and myself (Paton and Zaimis, 1951), and it will, I am afraid, be rather *vieux jeu* to some of the physiologists present.

Such a drug usually comes to notice by producing a fall in blood pressure, or, during stimulation of a preganglionic sympathetic nerve (which is quite commonly done in exploratory experiments) by producing a failure of the effector response. What is recorded is that at some step between the preganglionic nerve and the final effector organ a depression of function has occurred. How are we to disentangle the various possible causes? The first analytic step is to compare the effects of stimulating the pre- and postganglionic nerves electrically. This is done on the superior cervical ganglion, using the contraction of the nictitating

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membrance as a sign of ganglionic activity. First of all, you stimulate post-ganglionically. Then you stimulate through the preganglionic electrodes. During the latter you inject the drug under test, in this case hexamethonium. It produces a complete depression of the effector response, as shown by the absence of further relaxation when the stimulation is stopped. Now turn back to the postganglionic stimulation; it is as effective as ever. Return to the preganglionic trunk, it is still blocked. This shows that the drug has interfered with nothing "downstream" from the postganglionic electrodes; in other words, the muscle itself, the action of the peripheral transmitter, and its release, are all left unimpaired.

But we still have to distinguish between a drug which acts like hexamethonium and one which depresses acetylcholine release at the nerve terminals. One has to turn here to perfusion of the ganglion, so as to collect the acetylcholine released and to try whether the amount liberated by stimulation of the nerves before and during the presence of the drug being tested is changed or not. One finds that hexamethonium, even when injected in a relatively huge dose into a perfused ganglion (about the size of a pea), produces no reduction of acetylcholine output. Hence we conclude that the drug is what we are looking for in this case, something which specifically blocks ganglia by competitive antagonism with acetylcholine at the synapse.

All the work described has been done, of course, on a single ganglion. Since ganglia are known to differ considerably in their responses, it is obviously safer to conduct some tests on other ganglia. Unfortunately, one cannot do a rigorous analysis on any other preparation than the superior cervical ganglion; but good corroborative evidence can be obtained. Thus one can compare the response to stimulating the vagus nerve with the response to acetylcholine, using as test-object the rate of the heart. If the drug is a specific ganglion blocking agent it will paralyse vagal stimulation but leave the response to acetylcholine (which acts purely peripherally) quite unimpaired. It is found that hexamethonium does, in fact, behave like this. Similarly, you can compare the response to stimulating the ganglia by nicotine with the response of the blood pressure to adrenaline or to acetylcholine. Figure 1 shows such an experiment. First of all are three control responses to the three test drugs. Then in the middle panel some hexamethonium is given, producing, with a fairly small dose, a slow fall in blood pressure due to relaxation of autonomic tone. Further big doses produce no further fall, in itself a useful check that the drug does not have any further actions on the heart or circulation. Then we repeat the test drugs and find that acetylcholine can still lower the blood pressure, adrenaline can still raise it, but nicotine is now completely ineffective. You will probably have noticed that the responses to acetylcholine and adrenaline are changed, becoming prolonged, and in the case of adrenaline, increased. These, of course, are due primarily to the inactivation of the buffer nerves which normally check a rise or fall in blood pressure; when their influence is removed, then the rise or fall can be more prolonged and possibly greater.

From all this type of evidence one concludes that a drug like hexamethonium is a specific ganglion blocking agent and free of other actions.
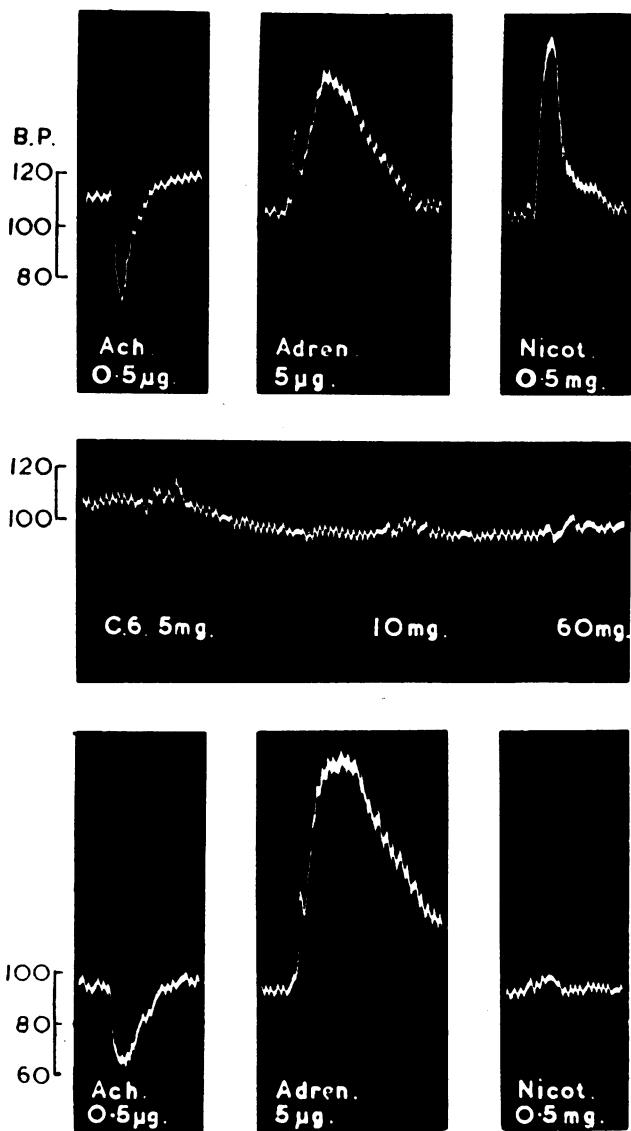
Fig. 1.

Records of the blood pressure of a cat anæsthetised with chloralose.

Top Panel: Normal responses to acetylcholine, adrenaline, and nicotine, given intravenously.

Middle Panel: Response to a medium dose of hexamethonium, followed by further large doses.

Lowest Panel: Response to acetylcholine, adrenaline, and nicotine after the hexamethonium.

(From Paton and Zaimis, 1951; by permission of the *British Journal of Pharmacology.*)

The knowledge whether a drug is specific or not is important; and I would like to mention two additional points about hexamethonium. First, one of the things that makes it specific is that it is a salt of quaternary nitrogen; without going into detail, this means that its molecules can only exist in solution carrying a positive charge—i.e., it is always fully ionised. Now such particles penetrate cell membranes only with difficulty. This gives to hexamethonium the following characteristic properties : poor absorption by mouth; distribution only in the extra-cellular fluid; resistance to metabolism; excretion by the kidney roughly like

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inulin (neither traversing the cells of the tubules outwards in secretion, nor inwards by reabsorption); and failure to enter the cerebrospinal fluid, which is quite a sensitive test (Fig. 2). This means that any central actions of hexamethonium (and they are not strong) are excluded by permeability considerations.

Secondly, one must remember that ganglion block does not always lead to quiescence of a structure. I remember being disconcerted to see how, in the cat
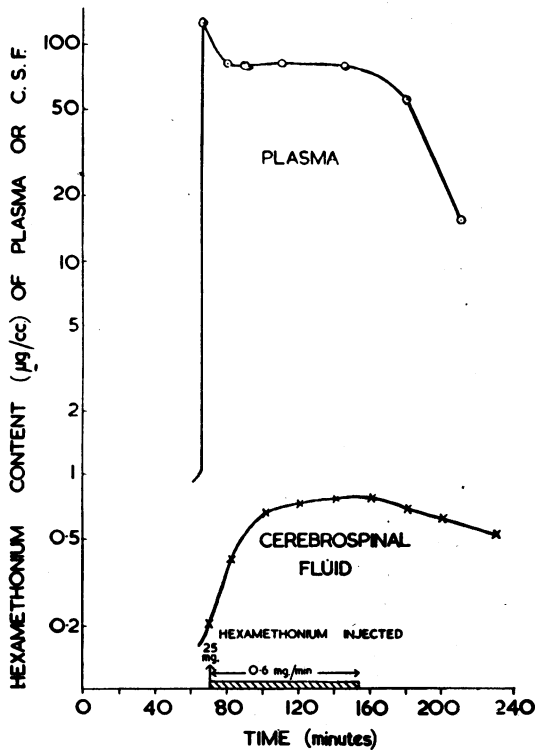

Fig. 2.

Comparison, in a cat anæsthetised with chloralose, of the concentration of hexamethonium in the cerebrospinal fluid with that in the plasma, during infusion of a large dose of hexamethonium.

(From Paton, 1952; by permission of the *Athlone Press*.)

under chloralose, hexamethonium and TEA can stir up the bowel (Fig. 3) (Paton and Zaimis, 1951). But this is not a muscarinic or histaminic action; it can be closely imitated by cutting splanchnic nerves—as described by Bayliss and Starling many years ago; and is due to release of intrinsic intestinal activity from sympathetic restraint, as hexamethonium paralyses the sympathetic ganglia.

OTHER GANGLION BLOCKING AGENTS.

Before going further, I ought to comment briefly on some of the other agents which resemble hexamethonium in action (Fig. 4). *Pentolinium* is now familiar, and resembles hexamethonium in all respects save for being more active and longer in its action. *Chlorisondamine,* likewise, is still more prolonged, possibly has a mild stimulant action on the colon, but is still like hexamethonium in principle

(Plummer, *et al.,* 1955, 1956; Smirk and Hamilton, 1956). With *mecamylamine* a new element comes in. For the first time we have an active agent, not quaternary, which can be present (although only in small amounts) in the uncharged form (Baer, *et al.,* 1956; Moyer, *et al.,* 1956; Doyle, *et al.,* 1956). As a result, it can penetrate membranes; it is well absorbed; it is distributed more widely than the extracellular fluid. There are hints that it may partly be metabolised. It is excreted in the urine in a rather interesting way : if the urine is acid (which increases ionization of mecamylamine in it), mecamylamine is rapidly eliminated (one supposes because it is not reabsorbed at all) : if the urine is alkaline,
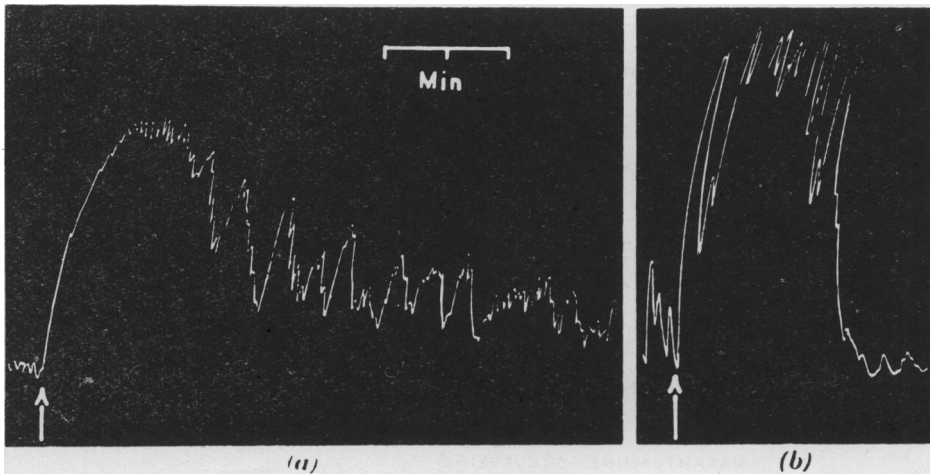

Fig. 3.

Cat, chloralose. Record of movements of small intestine. Intravenous injections. (a) At arrow, 0.24 mg. hexamethonium iodide per kg. (b) At arrow, 1.5 tetraethylammonium iodide per kg. (From Paton and Zaimis, 1951; by permission of the *British Journal of Pharmacology.*)

mecamylamine is very slowly eliminated (because now it can be reabsorbed). Thus a single circumstance (that of not being quaternary) makes oral administration convenient and duration of action controllable *in principle* (though it may not be worth doing in practice). One must note, however, that by the same token that mecamylamine is active by mouth, it may have an effect on the central nervous system : and it is in this direction, perhaps, which most care should be taken (cf. Doyle and Neilson, 1956).

The last blocking agent I would like to mention here is nicotine. I will not expatiate on the electrophysiological experiment which Perry and I did to study this type of action (Paton and Perry, 1953). Briefly, a drug like hexamethonium simply interferes with transmitter action—pure block; at the opposite extreme are drugs which imitate the action of the transmitter (like acetylcholine itself in excess) and, so to speak, throw the ganglion into a state of vigorous activity such that it can no longer respond to incoming signals—this is pure stimulant action. But

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between these extremes is a third; where a drug begins by stimulating, i.e., imitating the transmitter, and ends by blocking it; such a drug is nicotine; and Fig. 5 (which I promise is free from any electrical symbol!) may exemplify the differences mentioned.
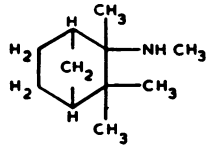
I have introduced nicotine because this mixed type of action runs through the whole of pharmacology; when you find that ergotamine is an adrenolytic yet contracts cerebral vessels, that drugs exhibit "tachyphylaxis," or that penicillin
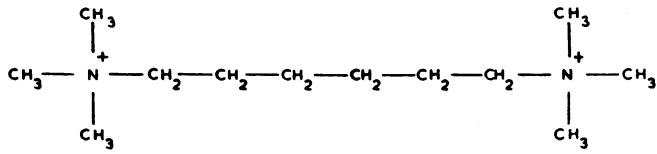
HEXAMETHONIUM

PENTOLINIUM

Fig. 4.

Structural formulæ of some ganglion blocking agents.
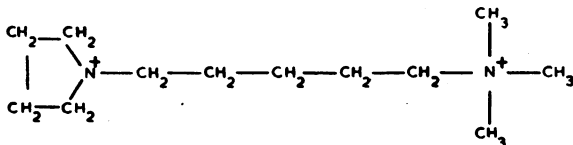
MECAMYLAMINE (INVERSINE)
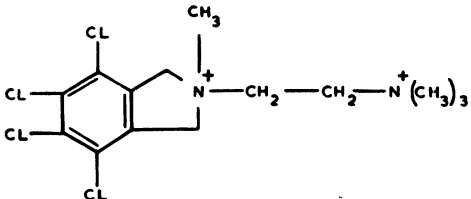
Chlorisondamine (Ecolid).

can sometimes stimulate the growth of organisms it usually inhibits, one is probably dealing with just this confusing but thought-promoting phenomenon.

REDUCTION OF THE BLOOD PRESSURE BY HISTAMINE RELEASE.

I would like to introduce this by discussing another drug which has been widely used for lowering the blood pressure at surgical operation to diminish bleeding, and is reputed to be a ganglion blocking agent. This is the material usually known as Arfonad, which has now received the official name "trimetaphan." If you inject it into an animal you find that it can, indeed, paralyse ganglia and part of its action seems undoubtedly like that of hexamethonium. But if you compare,

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for instance, the effect on the blood pressure in relation to that on the superior cervical ganglion (as measured by the contraction of the nictitating membrane) with similar responses obtained with hexamethonium you will see there is a considerable difference. In this particular experiment (Fig. 6) hexamethonium was able to produce a profound ganglion block; yet the blood pressure was little affected, because at the time there was little autonomic tone to be released. But Arfonad, while producing quite a long-lasting ganglion block, produced a distinct but transient change in blood pressure.

This blood pressure tracing is rather an interesting phenomenon. You can see the point of injection by a little spike (due to a momentary increase in venous
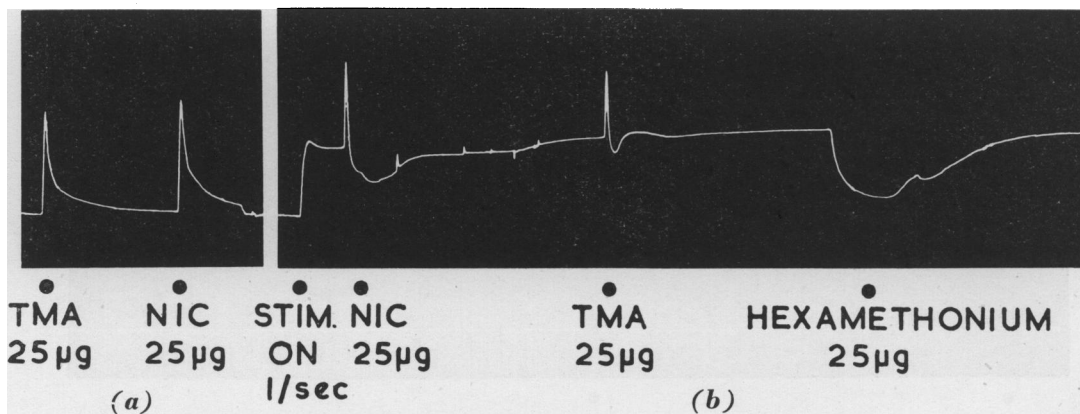

Fig. 5.—Responses of the nictitating membrane of the cat anæsthetised with chloralose.

(a) Comparison of tetramethylammonium (T.M.A.) and nicotine given intra-arterially into the blood-supply of an unstimulated ganglion, showing comparable stimulant action by both drugs.

(b) Comparison of nicotine, T.M.A., and hexamethonium given intra-arterially, while the ganglion is being excited by shocks at 1/second applied to the preganglionic cervical sympathetic trunk; showing the nearly pure stimulant action of T.M.A., the mixed action of nicotine, and the pure blocking action of hexamethonium.

return); then there is a latency of something like twenty seconds; finally, there is quite an abrupt but transient fall in blood pressure. This is a very characteristic example of what is called the "delayed depressor response," and it is characteristic of a group of drugs which MacIntosh and I worked on some years ago, the "histamine liberators" (MacIntosh and Paton, 1949). With many other compounds you will see the same picture with the blood pressure : the point of injection, then a latency, and then an abrupt fall followed by a recovery which depends on the dose given (Fig. 7). We found that the drugs themselves were not primarily active on the circulation; but that when they reached the tissues they released some of the histamine contained there, the histamine then circulated back in the veins, through the lungs and out again into the circulation, so that. the delay in the depressor

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response is simply equivalent to one circulation time. Histamine, of course, is quite a brief-acting drug, so that a histamine-liberator produces a fall in blood pressure and recovery which is not unlike that due to histamine itself, except that it is "stepped back" by the delay in the circulation time just mentioned. We proved that histamine release was occurring by showing that with a larger dose of the drug, histamine as such could be identified in the plasma.

If you inject such drugs intradermally they produce the triple response that Lewis described, a local erythema first of all which then develops into a weal with sometimes a red edge round it; and these two phenomena are accompanied

ARFONAD
3mg

HEXAMETHONIUM
0·4mg
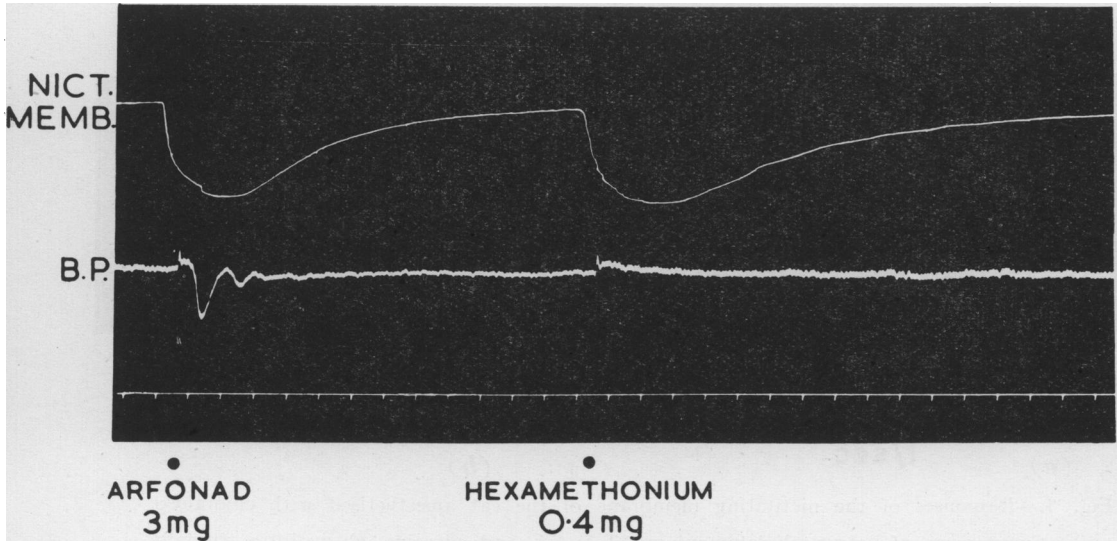
Fig. 6.—Comparison of the effect of Arfonad with that of hexamethonium (a) on transmission through the superior cervical ganglion, as tested by the response of the nictitating membrane to preganglionic stimulation at 10 shocks (second upper tracing) and (b) on the blood pressure (lower tracing) in a cat anæsthetised with chloralose. Injections are given intravenously.

by a third, the rather patchy flare extending two or three centimetres away from the point of injection. Arfonad will produce this reaction too. A decisive test for histamine release is to use cat's isolated perfused skin (Feldberg and Paton, 1951). This is a good preparation because the skin is full of histamine; yet the histamine is sufficiently firmly attached not to leak out during the handling of the skin which is involved in preparing it for perfusion. Further, you can perfuse it with a saline solution, so avoiding some awkward interfering substances present in blood. Figure 8 shows the effect of 100 μg of Arfonad in such a preparation; it releases something like 0.75 μg of histamine for each μg of Arfonad which was injected, quite a powerful release. To this we can add some of the known results reported by other people on the effects of Arfonad (Randall, *et al.,* 1949; McCubbin and Page, 1952). Thus Arfonad (like other liberators) injected into a dog can produce profound circulatory collapse with an engorged liver, a rise in portal

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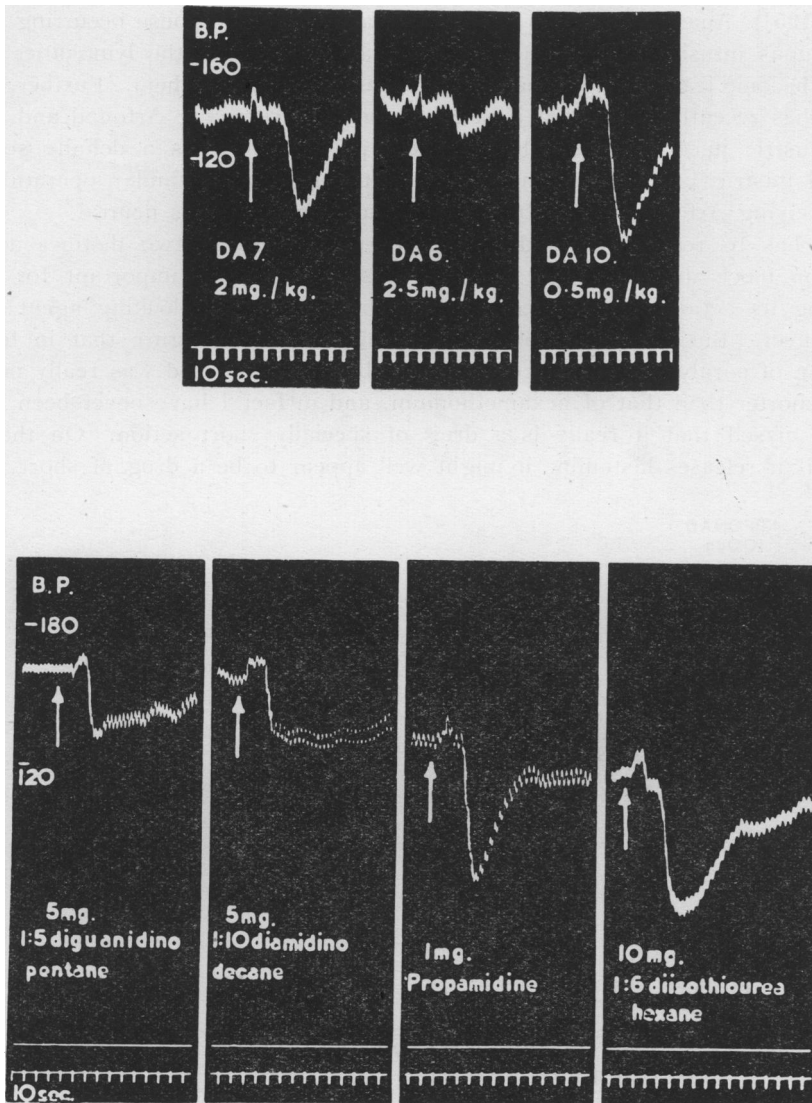
Fig. 7.—Responses of the blood pressure of the cat under chloralose to the intravenous injection of seven different histamine liberators.

(From MacIntosh and Paton, 1949; by permission of the *Journal of Physiology*.)

pressure and a change in coagulability of the blood—all the symptoms of anaphylactoid shock. There seems no doubt that Arfonad can, in fact, release histamine as well as blocking ganglia.

The question arises, of course, as to whether this release occurs in man. It is quite easy to show on one's own skin that quite a dilute solution of Arfonad will produce the weal and flare response which we have already mentioned (Mitchell,

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et al., 1951). Anæsthetists who look for it can see this response occurring during intravenous infusion of Arfonad; the vein and sometimes the lymphatics in the region become traced out by the urticarial response around them. Further, Payne (1955) has recently found that if you take patients receiving Arfonad and sample their gastric juice, you find that in these patients there is a definite secretion of acid gastric juice, although with patients undergoing similar operations but not receiving Arfonad the gastric juice remains more or less neutral.

One has to regard Arfonad, therefore, as possessing two distinct actions : ganglion block and histamine release. This seems to be important for understanding its action. It is often stated to be a ganglion blocking agent with a brief effect. But you will probably have noticed in the figure that in fact the duration of paralysis of the nictitating membrane it produced was really not very much shorter than that of hexamethonium, and in fact I have never been able to satisfy myself that it really is a drug of specially short action. On the other hand, if it releases histamine it might well appear to be a drug of short action;
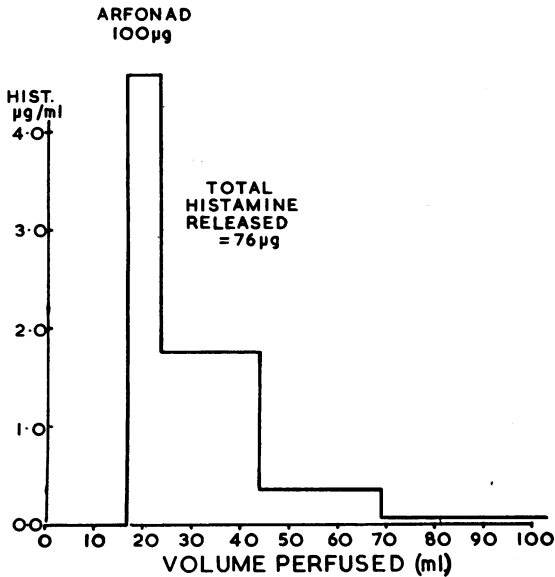
Fig. 8.
Release of histamine from a piece of cat's skin, isolated and perfused with Locke's solution, by Arfonad.

for as soon as it had completed its mobilization of tissue histamine the released histamine would be rapidly mopped up in the body, and the histaminic circulatory effects would indeed be rather transient. We have to think of Arfonad as being a drug with a potentially short action on the circulation, not because it is itself rapidly destroyed in the body, but because its action is that of histamine release on a background of ganglion block. When the infusion of drug is discontinued, the concentration of Arfonad begins to fall in the body, histamine release ceases, and the blood pressure begins to recover as the histamine is destroyed.

I have discussed Arfonad in some detail because it serves to illustrate two points. The first is that it is a neat example of a drug which, although it is a ganglion

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Records of contraction of the cat's nictitating membrane excited by stimulation of the preganglionic cervical sympathetic trunk at 1, 10 or 20 shocks per second (denoted by continuous, broken and dotted lines respectively). Above are the responses to these rates of stimulation, for one minute, in a normal cat. Below are the responses obtained after hexamethonium.

Increasing the rate of stimulation in the presence of hexamethonium does not necessarily lead to a bigger postganglionic response; although the change from 1/second to 10/second in (a) does so, the further acceleration from 10/second to 20/second in (b) actually produces (after an initial augmentation) a considerable increase in block.

AFTER HEXAMETHONIUM
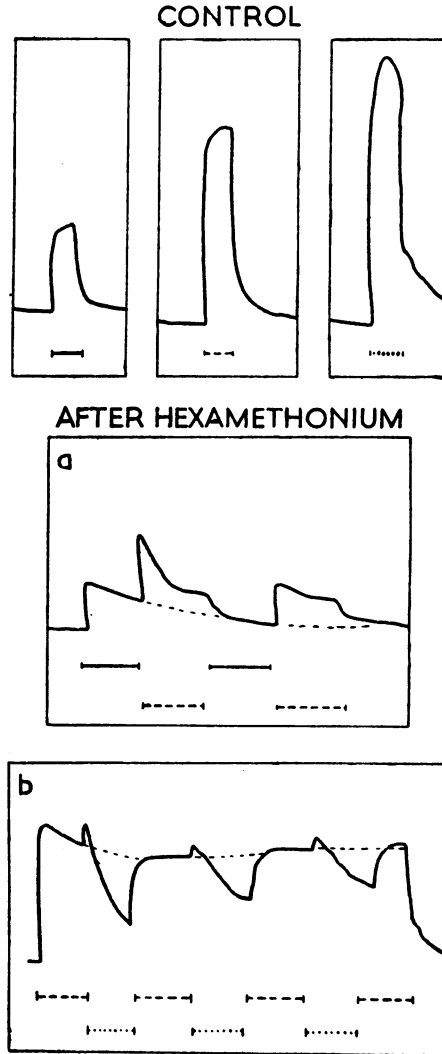
Fig. 9.

(From Paton, 1952; by permission of the *Athlone Press.*)

blocking agent, also has another action which can contribute to its circulatory effects. It shows the importance of making quite sure that a given effect which you have identified is, in fact, enough to account for *all* the actions of the agent. Secondly, it has allowed me to mention to you some of the main actions of the histamine releasing process. These are, in fact, quite widely diffused over a lot of drugs (for a review, see Paton, 1957). Thus, morphine, and some of the therapeutic diamidines used in trypanosomiasis (propamidine, stilbamidine and

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pentamidine) are histamine liberators. D-tubocurarine, the muscle relaxant, is quite a good histamine liberator, good enough, in fact, to be used as a standard drug for the purpose in many investigations. Strychnine, atropine and a number of other agents can also release histamine, but only in rather large doses compared to their ordinary therapeutic ones. Pethidine is a moderately active histamine liberator, and this may lie at the case of some of the urticarial responses described with it. All of these drugs can produce phenomena which look "allergic," yet need no previous sensitization, but simply the direct mobilization of the histamine locked in the mast cells of the tissues.

FACTORS CONTROLLING THE SENSITIVITY TO GANGLION BLOCKING AGENTS.

It is a striking fact about ganglion blocking agents that patients are rather variable in their response to them. Variations up to one thousand-fold exist between the dose which sometimes will produce a distinct effect and the dose which the clinician sometimes has to use to obtain the wished-for result. The causes of this variation are several-fold. The first one is that the effect of a ganglion blocking agent depends on the activity of the ganglia on which it is acting. In part this is simply a truism. Unless there is any autonomic tone existing in the organism you will see no effect when the autonomic pathways are blocked. Indeed, it is an interesting exercise to estimate, from the response of humans to ganglion blocking agents, what autonomic activity is normally in operation. One can summarize the result in the not too seriously intended "hexamethonium man."

"He is a pink-complexioned person, except when he has stood for a long time, when he may get pale and faint. His handshake is warm and dry. He is a placid and relaxed companion; for instance, he may laugh, but he can't cry because the tears cannot come. Your rudest story will not make him blush, and the most unpleasant circumstances will fail to make him turn pale. His collars and socks stay very clean and sweet. He wears corsets and may, if you meet him out, be rather fidgety (corsets to compress his splanchnic vascular pool, fidgety to keep the venous return going from his legs). He dislikes speaking much unless helped with something to moisten his dry mouth and throat. He is long-sighted and easily blinded by bright light. The redness of his eye-balls may suggest irregular habits and, in fact, his head is rather weak. But he always behaves like a gentleman and never belches nor hiccups. He tends to get cold and keeps well wrapped up. But his health is good; he does not have chilblains and those diseases of modern civilization, hypertension and peptic ulcer, pass him by. He is thin because his appetite is modest; he never feels hunger-pains and his stomach never rumbles. He gets rather constipated so that his intake of liquid paraffin is high. As old age comes on he will suffer from retention of urine and impotence, but frequency, precipitancy, and strangury will not worry him. One is uncertain how he will end, but perhaps if he is not careful, by eating less and less and getting colder and colder, he will sink into a symptomless, hypoglycæmic coma and die, as was proposed for the universe, a peaceful entropy death."

But the position is a little more interesting still. It also appears that the ganglion blocking agent can make the ganglionic synapse more easily fatiguable.

This means that if you increase the rate of stimulation, the proportionate block begins to become greater. One obtains a ganglion which may conduct fairly well at slow rates of excitation, but at faster rates it becomes quite deeply paralysed. At the top of Fig. 9 you can see the normal response to three rates of stimulation, 1/sec. 10/sec. and 20/sec. In the middle you see the response to 1/sec. and 10/sec. in the presence of hexamethonium. Now in this particular situation at 10/sec. you are still getting some further improvement on the contraction, although much less than normally. But if 10/sec. and 20/sec. are compared, you see that as soon as you switch over to the faster rate of stimulation the ganglion becomes more deeply paralysed; return to 10/sec. it recovers; stimulated faster

Fig. 10.—Distribution of ganglion block over nine autonomic functions in forty-one subjects. The left-hand column gives the function tested; S or P indicate whether it is sympathetically or parsympathetically controlled. On the vertical lines, one for each subject, a filled circle is given where the effect of hexamethonium 25 mg. subcutaneously exceeded a certain magnitude, for each function tested.

(From Paton and Steinberg, 1956; by permission of the *British Medical Journal.*)

again it becomes more deeply blocked. This has the important consequence that ganglion block will "pick out" those pathways which are being driven particularly fast, but leave those which are proceeding at a quieter rate relatively unblocked. I suspect this type of phenomenon explains some of the exaggerated responses to ganglion blocking agents which are described from time to time.

A second important factor in the sensitivity of ganglia to blocking agents is that they seem to differ in their responsiveness. In animal this is quite striking; indeed Langley more than fifty years ago first described the phenomenon with nicotine. Similarly with hexamethonium, it is much easier to paralyse the fibres to the pupil than it is the nictitating membrane. In a whole animal it is easier to paralyse salivary secretion than the activity of the vagus nerve; there are many other similar examples. The same is true in man; I would like to illustrate this with some results (Fig. 10) in an experiment which Miss Steinberg and I did at University College in a students' practical class (Paton and Steinberg, 1956). The students were arranged in teams of four with one volunteer receiving the drug (25 mg. hexamethonium s.c.) and three making systematic observations of various autonomic functions. Then we analysed the results, according to whether there had been a significant effect on particular autonomic functions studied or not, and the figure shows the results on forty-one students on which satisfactory

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records were obtained. The outstanding thing about this experiment is that every student had a different pattern of autonomic block. Some would have a postural hypotension, to the verge of fainting, without any effect on the pupil or the reaction to accommodation. Others would have quite a marked effect on the eyes and yet very little effect on the blood pressure. It was remarkable that even in a single ganglion, the ciliary ganglion, you might find paralysis of the pupil and not of accommodation, or paralysis of accommodation and not of the pupil; it seemed as though you could produce a sort of Argyll-Robertson pupil or inverse Argyll-Robertson pupil according to the individual. One has therefore to allow for a substantial variation from one individual to another, and from one ganglion to another.

An analogous point is this, that it is difficult to produce complete block with these drugs. If, for instance, you give maximum doses of hexamethonium to an anæsthetised animal, you will still fail to lower its blood pressure as far as can be done by destroying the spinal cord; and there are other examples illustrating the difficulty of paralysing *all* the ganglia in the body. Now there is an analogous clinical situation here, in the difficulty met by the surgeon undertaking sympathectomy. There are many ganglia in the sympathetic system which are not located in the sympathetic chains normally drawn in the text books, but are hidden away in spinal nerves, in rami communicantes, sometimes found approaching the spinal canal itself (cf. Boyd and Monro, 1949). Now we know that hexamethonium, and quaternary salts like it, penetrate into the cerebrospinal fluid only with great difficulty, so that it cannot reach structures which are definitely within the cerebrospinal axis. But we know also that it can reach ganglion cells in the superior cervical ganglion, and in the heart and in the intestine, and so on. The interesting question arises as to where the barrier to diffusion of these quaternary salts disappears as you move out from the central nervous system to the peripheral nervous tissue. It seems quite possible that the change of accessibility of ganglia to compounds of this sort is not abrupt as you come through the vertebral laminæ, but may actually occur somewhere along a nerve trunk; so that any ganglion cells which have not been fully extruded into the normal sympathetic chains may, in fact, be simultaneously inaccessible, and for the same reason, not only to the surgeon's knife but also to the pharmacologist's syringe.

THE RESPONSE TO SYMPATHECTOMY.

This brings me to a rather different topic. I mentioned that one of the surgeon's difficulties in sympathectomy is that he cannot remove all the sympathetic ganglia. It was shown quite a long time ago by Simeone, Cannon, and Rosenblueth that if you cut the majority, but not all, of the preganglionic fibres to a ganglion there is a remarkably rapid recovery of function. Recently Murray and Thompson (1957), in my laboratory, have been re-examining this phenomenon. Figure 11 illustrates what happens. Supposing you cut down the number of fibres in the preganglionic trunk of the cervical sympathetic in the neck by sectioning the rami where they leave the spinal nerves from the thoracic 1, 2, and 3 segments. This means that the remaining fibres, contributed by segments T4-7, now are the only ones

supplying the superior cervical ganglion. T1, 2, and 3 contribute about 90 per cent. of the fibres, T4-7 the remaining 10 per cent. If you stimulate the residual 10 per cent. in a normal ganglion only a small ganglionic response detectable, and electrically there is a much reduced ganglion action potential. But if you now wait for five or six weeks and then repeat the experiment, again stimulating the residual 10 per cent. coming from T4-7, you find that there is an enormous recovery of
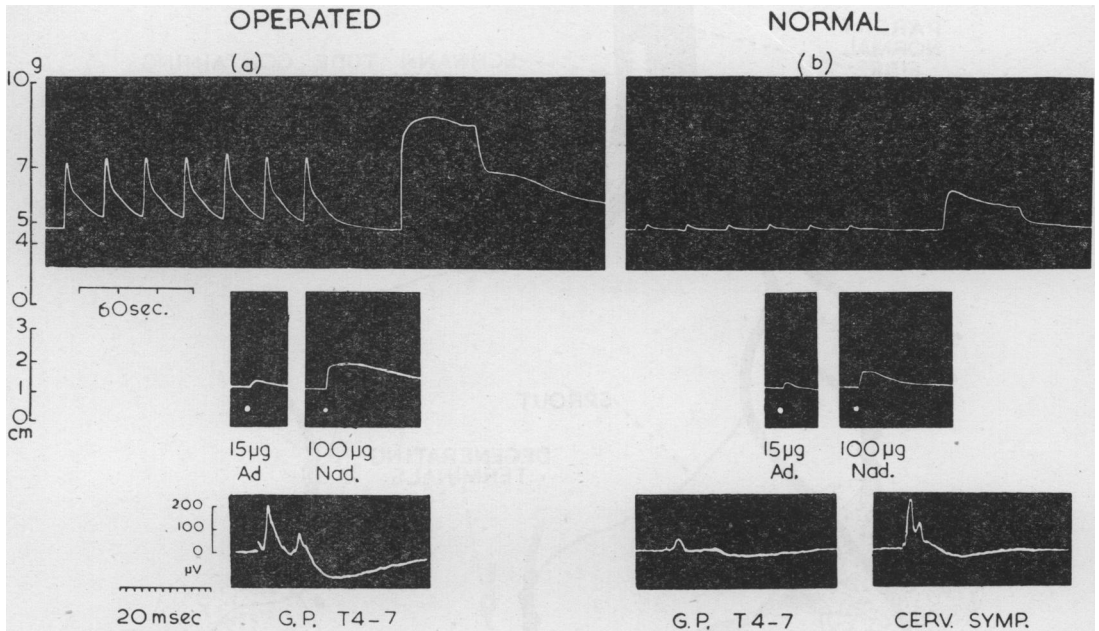

Fig. 11.—*Upper Panels:* Responses of the nictitating membranes of a cat anæsthetised with chloralose on (a) the operated side, on which rami T1-3 had been divided forty-nine days previously, and on (b) the normal side. The smaller responses are due to four shocks at one shock/second delivered every minute, the larger responses to shocks at 10/second for two minutes, the shocks applied to T4-7 on both sides simultaneously.

Middle Panels: Contractions of the nictitating membranes on the two sides to intravenous adrenaline and noradrenaline, showing absence of supersensitivity on operated side.

Lowest Panels: Records of ganglion action potentials (G.P.) from another animal in which, on the operated side, rami T1-3 were cut seventy days previously. In (a) T4-7 are stimulated; in (b), first T4-7, then the whole preganglionic trunk.

(From Murray and Thompson, 1957; by permission of the *Journal of Physiology*.)

function. The contraction of the nictitating membrane is normal; the action potential is as large as originally.

Now the question arises as to how this return of function has taken place. Firstly, it cannot be attributed to regeneration from the sectioned rami; the time is far too short. Nor is it due to supersensitivity; this appears earlier, but it

disappears as recovery of function becomes complete; and in the figure you will see a test of the response of the nictitating membrane to adrenaline and nora-adrenaline, showing the responses hardly distinguishable from normal. So that one requires some mechanism for return of function which does not depend on regeneration of the damaged fibres nor on sensitization of the structures whose nerves have been interfered with.
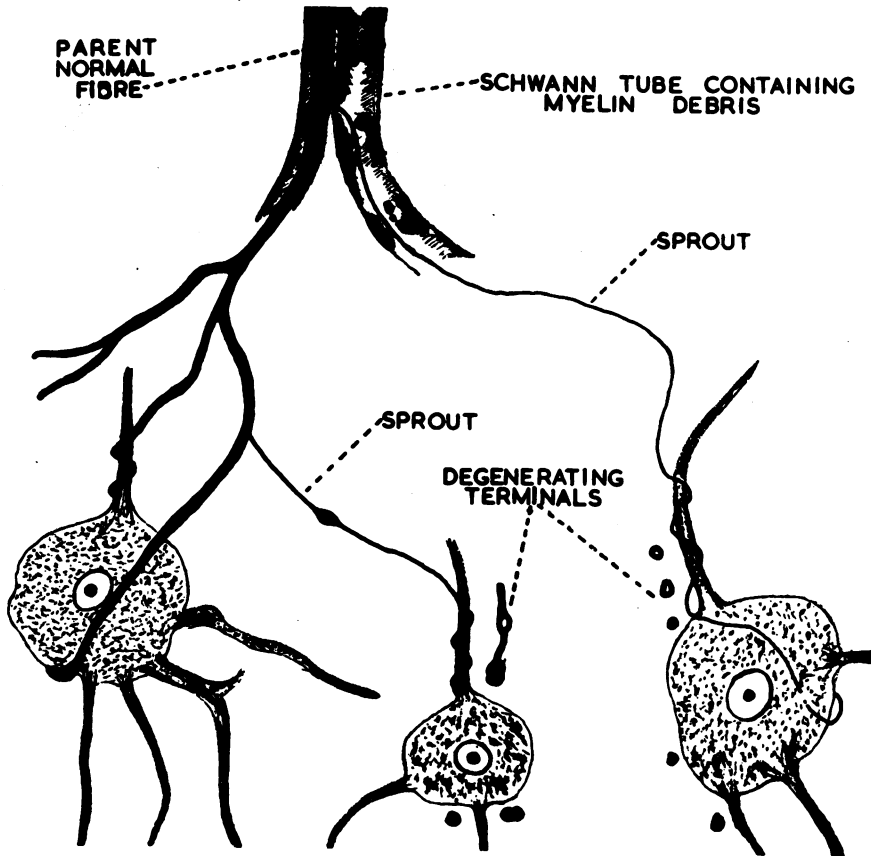

Fig. 12.—Diagram of an area of superior cervical ganglion of the cat, five days after section of rami T1-3, showing two sprouts arising from a normal parent preganglionic fibre, and typical fragments of degenerating preganglionic terminals.
(From Murray and Thompson, 1957; by permission of the *Journal of Physiology*.)

The answer lies in the part played in the recovery by the remaining *normal* fibres. These begin to give off little "sprouts" as they are called, small axoplasmic shoots which enter the Schwann tubes of the degenerating nerves. These tubes then guide the sprouts to the deprived ganglion cells and reinnervation takes place by these means. The process of sprouting is a very rapid one, and is histologically obvious within four or five days from the first section of some of the sympathetic

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preganglionic fibres (Fig. 12). The efficiency of the sprouting is enormous since it can, as we have just seen, allow 10 per cent. of the fibres to restore the function of the whole.

You will probably have suspected the occurrence of a rather interesting feature of this form of response to injury. The fibres which were left behind, the residual 10 per cent., normally innervate only a particular group of ganglion cells. In the present circumstances they normally do not run to the ganglion cells supplying the pupil at all, but only to the nictitating membrane and to vascular structures and hair follicles. But if sprouts from them enter channels normally traversed by other nerve fibres they are liable to be brought into communication with ganglion cells which they do not normally touch. This is shown rather nicely by the fact that, after the process of sprouting has developed, the residual 10 per cent. of fibres now begins to be able to produce a transient dilatation of the pupil; as the sprouting develops this dilatation becomes better and better sustained and finally approaches the normal response. Thus the phenomenon brought about by sprouting is not only a return of function, but also a redirection, a "re-routing" of the autonomic nervous system, such that preganglionic fibres come to innervate additional and novel structures.

Murray and Thompson have gone into some of the other properties of these sprouted fibres, one of which I would like to mention. The synapse made by the sprouted fibres is more sensitive than usual to ganglion blocking agents. A dose of hexamethonium which normally has little effect on the nictitating contraction will have quite a substantial effect when tested against a contraction of similar height but mediated by a sprouted system. This last observation probably serves to explain one of the rather interesting results which have been reported following sympathectomy. Sometimes surgeons have sympathectomized a patient for hypertension, and found that, after a period of reduced blood-pressure, the hypertension returns, and in a time rather soon for regeneration. This is itself odd; but the situation is made odder still by finding that in these patients, in which presumably the autonomic nervous system is much reduced in importance, they are still sensitive or even hypersensitive to ganglion blocking agents. From what I said earlier, however, about the existence of accessory ganglia, you will have recognised that sympathectomy provides a happy hunting-ground for sprouting (if I may mix my metaphors). Wherever you get ganglionic pathways which are unimpaired adjacent to others which are sectioned, there will be possibility of restoration of function in the damaged fibres by sprouting from the residual ones. This may well explain the return of function after apparently successful sympathectomies. Further, the observation which Murray and Thompson made about the special sensitivity to hexamethonium would again lead one to expect that these patients, after return of function, should still be sensitive or more sensitive to such blocking agents.

There is another aspect of the sprouting story which I think will deserve a good deal of exploitation. As one looks through the field of clinical surgery in the sympathectomy field and through some of the curious physiological oddities following denervation which have been recorded, one realises that the possibility

of sprouting is a very important one to take into account. One can expect, I think, fairly confidently that sprouting of this sort may occur wherever nerves of similar types come into relationship. By this I mean that supposing a sympathetic preganglionic trunk is sectioned, if there happen to be other cholinergic nerves in the vicinity then these, as well as another sympathetic preganglionic trunk, may well sprout and establish effective connection with the ganglion cells which have been deprived of their nerves. If one takes the clinical phenomenon of gustatory sweating, for instance, it is not impossible that sprouts grow from axons normally involved in gustatory responses into the sympathetic preganglionic pathways left behind after a sympathectomy. Likewise, the Sherrington phenomenon, the Rogowicz phenomenon and the Philipeaux-Vulpian phenomenon, conditions where contractures follow the excitation of nerves which are not normally motor, may involve the ingrowth of cholinergic nerves into trunks which have been deprived of their normal nerve fibres. The more one digs below the surface among the sequelæ to operations of denervation, the more one appreciates that the sprouting of one set of intact nerve fibres into the degenerating Schwann tubes of another set is a consideration to be taken very seriously. The autonomic nervous system is extraordinary not only in the versatility of the reactions which it mediates, but also in the effectiveness of the repair process which takes place when it is damaged.

THE CONSEQUENCES OF LOWERING THE BLOOD PRESSURE.

I would like now to be somewhat speculative (and correspondingly vulnerable) in comparing what can be regarded as two main methods of lowering the blood pressure. On the one hand, one can take a group of procedures such as spinal anæsthesia, ganglion block, or the administration of a drug which paralyses the peripheral sympathetic terminations. By all these manœuvres one can obtain a profound fall in blood pressure, and a marked sensitivity to posture; but the circulating blood volume is normal, and there is a peripheral vasodilation. Despite the low blood pressure, blood flow to many of the organs may be normal or even increased. On the other hand one has a group of procedures which may lead to what is called "shock." This includes hæmorrhage, histamine infusion or release in large amounts, traumatising a limb or prolonged application and then release of a tourniquet, the effect of burns or the crushing of the skin or of a limb. In all these and in other cases there is a reduction of the circulating blood volume, either by frank withdrawal of blood, or by leakage of fluid into tissue spaces out of the circulation; and there is also a vigorous sympatho-adrenal response. The total result is an intense vasoconstriction, so that even though the blood pressure may be partly restored by this reaction, the blood flow to essential areas may be quite seriously cut down. It is quite clear, for instance, that after these procedures the circulation through the gut, the kidney, the liver and the skin, and possibly sometimes the heart and brain, are quite considerably reduced. There is a very curious phenomenon which occurs with the second group of reactions which does not seem to occur, or has not yet been observed with the first group of hypotensive procedures. This is the phenomenon known as "irreversible" shock, meaning by this simply that the hypotension and peripheral circulatory failure become incurable

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whatever treatment you care to give; and it is liable to occur whenever the shock persists longer than a few hours. If I may be frivolous for a moment; I hope you will not think the concept of irreversible shock is a modern one. That incomparable physiologist, Jane Austen, describes it in Sophia's dying words to Laura : "Beware of fainting fits. . . . Though at the time they may be refreshing and agreeable yet believe me they will in the end, if too often repeated and at improper seasons, prove destructive to your constitution. . . . A frenzy fit is not half so pernicious."

This phase of irreversible shock is one of which a good deal of work, some of it rather uncritical, has been devoted (cf. Green, 1953). The possible causes of the irreversible phase which have been canvassed include (1) the release of vasodepressor material (identified by at least one group of workers as the material called ferritin which is involved in iron metabolism); (2) the growth of anærobic organisms in the liver with production of toxins; (3) a hypercoagulability of the blood and formation of "micro-clots" in the circulation with progressive occlusion of blood flow in lungs and elsewhere; (4) chronic tissue anoxia with liberation of unspecified toxins or local damage to cells. None of these possibilities can be either proved or excluded on the evidence at present available. But the point which I would like to make now is that all of them can be regarded as flowing from the exaggerated vasoconstriction which follows such "shock" procedures. Clostridial organisms can flourish in an ischæmic liver, blood clots form more easily in a slowly flowing stream; ischæmia of tissue certainly releases vasoactive materials.

ADRENALINE SHOCK.

We have then two conclusions, the first that if hypotension is produced by a method which, amongst other things, inactivates the whole sympatho-adrenal discharge, then it appears to be relatively safe for prolonged periods; but on the other hand, with other types of hypotension which this discharge is called into being and is intense, the hypotension may become irreversible. Secondly, the theories which are called into play to explain the irreversibility all seem to focus one way or another on the vasoconstriction as being the damaging factor.

I would like to mention here a third point to consider, the rather interesting and neglected phenomenon known as adrenaline shock. Continuously or massively administered adrenaline is quite dangerous. This was first recognised in the 1914-18 war and has been repeatedly confirmed (Bainbridge and Trevan, 1917; Erlanger and Gasser, 1919). If a massive dose of adrenaline was injected into the liver, for instance, a syndrome not unlike that of anaphylactic shock occurred. A very interesting study was made by Blackett, Pickering, and Wilson (1950), in which they compared the effects of infusing continuously adrenaline, noradrenaline and renin into unanæsthetised rabbits. They found that with adrenaline and noradrenaline the requirement of these hormones to produce a given blood pressure continuously rose and that when the infusion ceased the blood pressure fell abruptly and approached lethality. But this lethal process did not depend upon the height of the blood pressure or the vasoconstriction producing it, since a satisfactory hypotension could be easily maintained with renin for as long as was desired;

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and when the infusion stopped the blood pressure returned quietly to normal. Later it has been found that with continued administration of adrenaline a defect of capillary permeability may appear, leading to a loss of plasma to the tissues and there may be hæmorrhages in the pericardium and in the intestine (Freeman, et al., 1941). It is clear that this danger of adrenaline shock is more intense with adrenaline than with noradrenaline. On the *practical* side it seems to be relatively easily avoided by using noradrenaline if an agent of this sort is required, and by seeing that when the infusion is stopped the drug is slowly tapered off and not abruptly removed. But it is significant that the continued administration of these natural substances, a thing which may well be happening during a prolonged sympathoadrenal discharge in "shock," may in fact be quite deleterious to the body. In fact one wonders whether part of the so-called irreversible stage of shock may be marked not so much by some new event to do with the shocking process, as by a development of adrenaline shock as a consequence of an overactive and too prolonged reaction to the body to the original damage.

To all this we can add a last bit of evidence which seems to be slowly becoming clear. If you subject animals to hæmorrhagic or other types of shock, corresponding to those occurring in man, they seem to survive better if their sympatho-adrenal reaction is blocked. Thus dogs treated with dibenamine may enter the irreversible stage of shock less readily (Remington, et al., 1950; Lotz, et al., 1955). Rats in which tourniquet shock is produced may survive better if treated with hexamethonium (Spoerel, 1955). There is another rather different example which is interesting; if you poison mice with anticholinesterases you find that after treatment with hexamethonium they may be protected as much as ten-fold against the poison, protection which may in fact considerably exceed that afforded by the conventional antagonist atropine (Parkes and Sacra, 1954). So there is evidence that if you remove this particular response of the body to various stressful situations, then so far from survival being impaired, it may in fact be improved. I think it is not unfair to mention too the interest taken in procedures such as cooling and ganglion block, and the use of central depressants of various sorts to make a patient *more* fit for various operative procedures, yet with the expressed intention of abolishing the autonomic responses.

The Physiological Significance of the Autonomic Nervous System.

The conclusions I have just been outlining, if they are followed to a logical conclusion, produce the rather disconcerting result that the autonomic nervous system may be a substantial liability to the body, and it is this last possibility which I would like briefly to examine. The usual teaching about the sympatho-adrenal system is based on the work of Cannon and is expressed in the classical statement that it is a system which confers an advantage on the organism when it meets emergency of some sort, resulting in the need for staying to fight, or taking flight, or expressing fright. It is fairly obvious, I think, from several lines of study that the system is not essential for ordinary life. Cannon (1930) himself showed that, after the sympathetic nervous system had been ablated, a cat could still lead a relatively normal life. It is true that he probably did not remove as

much of the system as he thought, in the light of our new knowledge about accessory ganglia, but there was no doubt that he did attenuate it considerably. Similar work has been done on the dog yielding quite similar results (MacDonough, 1939).

Added to this you can consider the progress of patients who have been sympathectomised or treated with ganglion blocking agents. It is true that their activities are somewhat modified and there are a number of side actions accompanying ganglion block to which adaptation is needed. But if you think of other structures of the body such as the adrenal cortex, the pituitary gland, the kidneys, or the liver, you can immediately recognise that the autonomic nervous system does not occupy a point of comparable vital importance. One could fairly suggest that whatever the autonomic nervous system's importance may have been for some lower organism, it no longer occupies such a key position for mammalian life, or in particular for human life. Indeed, its presence may in fact confer a liability, in that it makes possible the play of emotion of all sorts of our viscera, and so gives rise, perhaps, to the psychosomatic diseases, and conditions such as peptic ulcer and hypotension in their neurogenic aspect. It is worth while to balance up mentally (though, of course, artificially) the physiological loss which would be incurred by abrogating our right to an autonomic nervous system, against the clinical gain by the number of diseases from which we would be freed.

But, of course, Cannon's view on the sympathetic was that its rôle was not in normal life but under emergency conditions. I think it is this concept particularly which has been eroded of recent years. I do not see how one could predict, if this was really true, that the inactivation of the sympathetic by dibenamine or the paralysis of autonomic ganglia by drugs should really favour survival in situations such as hæmorrhage, tourniquet shock or poisoning with anticholinesterases; or that the human organism should be more ready for elaborate and taxing surgical operation when all its autonomic defences are shattered by refrigeration and whole batteries of paralytic cocktails. One gains, instead, the impression that the autonomic system is an evolutionary heritage which, however useful in our ancestral past, now seems to be out of gear with the requirements of human social life with its continued and varied emotional pressures. This is a philosophical, and nearly untestable idea. Yet I personally find it a stimulating one, as well as one which can produce heated argument. Certainly it serves to show that we cannot, even now, give a satisfactory account of the system—not even of the reactions to a fall in blood pressure; and to remind one how much there is still to do in a field in which—as does not always happen—the pharmacologist and the surgeon can happily and profitably hunt together.

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