on matters connected with the promotion of health, and many of these have been taken up by the Government—usually, however, after years of delay—and incorporated in Acts of Parliament. Of such was the Medical Inspection of School Children Act. Years before the State began to take any great interest in the promotion of health the Council of the Association appointed a committee to collect reports from a large number of medical practitioners on the health of young children. Many thousands were examined voluntarily, and a large number were found to be suffering from the effects of illnesses for which they had never been medically attended, as the parents had not considered these bad enough to require medical attendance. Obviously, however, they were sufficient to lay the foundation of future ill-health, if not serious disability.

On the information supplied a report was drawn up which presented a very strong case—incontrovertible, indeed—for the institution of school medical inspection. This report was presented to the Government of the day, but it was over ten years before the School Medical Inspection Act was passed. It is freely acknowledged that the Act has been of profound benefit from the earlier recognition of ill-health or disability in children, thus allowing earlier treatment to be instituted. There is still lacking in some quarters any proper liaison between the family doctor and the local health authority which administers the Act. Neither State nor municipality yet recognizes or uses to its full value the service which the general practitioner can give and is giving in the way of instruction to his patients on the prevention of disease and the promotion of health. A similar report was issued in 1909 regarding ophthalmia neonatorum, and compulsory notification was strongly urged in that report. This was adopted by the Government in 1914. A long list of similar events could readily be given, but I will mention only one, which was possibly unique because the Association on that occasion was asked by the Government to present a report on physical education.

Our great Association, with its Empire-wide connexions and influence, has in the past played a notable part in the promotion of health, and one feels confident that so long as it continues to attract to its Council men of knowledge, public spirit, wisdom, and vision, its accomplishment in that direction in the future will transcend all its past achievement.

At the last quarterly court of the directors of the Society for Relief of Widows and Orphans of Medical Men one new member was elected, and it was reported as an interesting fact that the candidate was, on his father's side, the great-great-grandson of the first president of the society, Sir George Baker, President of the Royal College of Physicians of London, 1785-90; 1792-3; and 1795, who was elected president of the society in 1788, and on his mother's side he had a similar relationship to Dr. Ware, who was elected second president of the society in 1810. A sum of £2,425 was voted for the payment of the half-yearly grants to the sixty-two widows and four orphans in receipt of relief, which is granted only to the widows and orphans of deceased members. Membership is open to any registered medical man who at the time of his election is resident within a twenty-mile radius of Charing Cross. Many applications for relief from widows of medical men have to be refused because their husbands had not been members of the society, and the directors cannot too strongly impress on newly qualified or newly married medical men the advantages that may be obtained by joining the society. Full particulars may be obtained from the secretary at the offices, 11, Chandos Street, Cavendish Square, W.1.

THE PHARMACOLOGICAL ACTIONS AND THERAPEUTIC USES OF SOME COMPOUNDS RELATED TO ADRENALINE*

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LECTURE II: THERAPEUTIC USES

The synthesis and pharmacological investigation of compounds related to adrenaline have been carried out partly with the utilitarian object of finding improved substitutes for adrenaline in its various therapeutic uses. It is convenient, therefore, to examine briefly the established therapeutic uses of adrenaline and to consider to what extent new compounds have replaced or supplemented adrenaline itself or have provided new and independent therapeutic uses.

Actions on the Circulation

Under most conditions adrenaline, intravenously injected, produces a steep and sudden rise of pressure, lasting only a few minutes. It produces a less pronounced rise when given intramuscularly, and usually little or no pressor effect but possibly cardiac acceleration when injected subcutaneously. It is inactive given by mouth. The rise of pressure is due, in the normal animal, mainly to vasoconstriction. The arterioles of the skin, mucous membranes, and splanchnic viscera (except those of the intestine) are constricted. The vessels of the muscles and heart are actively, and those of the lungs and brain passively, dilated. While these statements can be taken as generally true, there seem to be considerable variations in different species of animals in the distribution of vasoconstrictor and vasodilator fibres to different tissues. It is important to remember that adrenaline does not raise blood pressure by general vasoconstriction. It causes, rather, a redistribution of the blood in the direction of increasing the amount in the heart, lungs, muscles, and central nervous system at the expense of the skin and abdominal viscera. The heart rate may be reduced, mainly owing to stimulation of the vagus centre by the rise of blood pressure. When the heart is feeble and the blood pressure abnormally low, cardiac stimulation may play a more important part in the pressor action.

There are some advantages in considering the vascular and cardiac actions of adrenaline separately, though it will be realized that both vascular and cardiac failure may coexist clinically and, even if one alone is primarily at fault, the other will be secondarily involved.

Pressor Actions

The first point for consideration is what value, if any, do adrenaline and related compounds possess in conditions of vascular failure, especially in so-called shock. It is not altogether fortunate that the word "shock" came to be used in its present connotation. The word implies a sudden and violent effect, whereas many cases of shock may be of gradual onset, and further suggests an emotional element which may be absent. In various kinds of bacterial intoxication, or as the result of injuries, burns, operative procedures, etc., circulatory failure is common. In many, probably most, of these conditions the circulatory failure is not primarily cardiac but is due to

* The Oliver-Sharpey Lectures delivered before the Royal College of Physicians of London on March 21 and 23, 1939.

dilatation of the vessels or to diminished blood volume resulting from escape of fluid from the blood, or to a combination of both these factors. The logical treatment for loss of blood volume is infusion with gum saline or glucose solution, or transfusion with blood. So far as vascular dilatation is concerned much evidence goes to show that in these conditions of intoxication the dilatation affects especially the capillaries. Adrenaline acts mainly on the arterioles and is therefore unlikely to be very efficacious in remedying the condition. The transient nature of the pressor effect of adrenaline is also a factor against it, but many related compounds produce far more sustained effects. Here again, however, the latter are unlikely to be of much value unless they act upon that part of the circulation which is primarily at fault. In actual experience drugs of the adrenaline group have been disappointing in the treatment of circulatory failure due to toxins. The pressor principle in pituitary extract is believed to have more effect on the capillaries than adrenaline, and would therefore seem, *a priori*, to be more suitable as a pressor agent in these conditions. Dr. Bazan, working in my laboratory, has recently found that, in the vascular failure resulting in laboratory animals from poisoning with snake venom or ricin, which are allied to bacterial toxins, pituitary extract is more efficacious in restoring blood pressure than adrenaline, ephedrine, or related compounds.

It is pertinent in this connexion to appreciate the fact that the action of toxins is apt to be prolonged and that, once a toxin had attached itself to a tissue, it is with difficulty dislodged. A familiar example of this is that, if an animal receives a bare minimal lethal dose of cobra venom with resulting paralysis of respiration, artificial respiration can keep the animal alive for many hours, but without any sign of recovery of natural respiration. Recovery from the action of toxins is, in fact, generally a slow process, and there is the less hope, therefore, for any substantial gain from the temporary stimulus than can be administered by drugs.

Recovery from the poisonous effects of drugs may be, on the other hand, very rapid. Their action is more easily reversible and they are eliminated more quickly from the tissues; consequently they can be more readily antagonized by drugs which have a transient action. Especially in acute experiments with drugs which produce a profound fall of blood pressure, it is a common observation that adrenaline may restore the blood pressure to normal. Moreover, adrenaline may under those conditions produce a permanent effect by interrupting a vicious circle. As the result of the rise of blood pressure the heart itself, as well as the vasomotor and respiratory centres, receives a better blood supply, and this temporary fillip may be sufficient to maintain the improvement when the primary direct effect of adrenaline has worn off. Dr. Simonart and I (1930) illustrated such an effect in an animal poisoned by harmalol. The dose given arrested respiration and lowered the blood pressure to 10 mm. Hg. After artificial respiration the normal respirations were resumed and blood pressure rose gradually to 30 mm. Hg. An injection of adrenaline then raised the blood pressure to 92 mm., with a coincident increase in the rate and depth of respirations. The rise of blood pressure was continuously maintained for three hours, when the experiment was discontinued. Heymans and Bayless (1937) have recently shown also that, with veritol, in certain experimental conditions the blood pressure once raised stabilizes itself there indefinitely. Conditions of low blood pressure can exist, therefore, though probably of infrequent occurrence clinically, in which a single dose of adrenaline may produce a permanent improvement, so that the brevity of

its effects in the normal animal is not necessarily a bar to its employment in certain conditions of abnormally low blood pressure. Nevertheless there are undoubted advantages in using a drug that will directly produce a more enduring elevation of blood pressure, and, as has been discussed in the review of their pharmacology, many compounds related to adrenaline are known to produce a more lasting pressor action than adrenaline, and some have been used therapeutically for this purpose. Of these, ephedrine has been most widely used, especially to combat the fall of pressure that may occur with the use of spinal anaesthetics.

In the comparison given in the first lecture of the action of various compounds on the blood pressure account was taken merely of the net effect on the level of blood pressure. When a more detailed analysis of the action on blood pressure has been made, it has been found that compounds differ not only in intensity and duration of pressor action but in the events that are transpiring during the rise of pressure. Thus Crismon and Tainter (1938) found with different compounds different ratios of the cardiac and vascular components in the pressor action. Moller (1937) states that there are certain fundamental differences between the action of adrenaline and corbasil, especially that the latter dilates the vessels of the kidney and increases the volume of the spleen, whereas adrenaline has the opposite effect in both cases. Other examples could be quoted, but these may suffice to emphasize the fact that the measurement of a pressor effect does not give a sufficient indication of what is the underlying redistribution of the circulation that takes place when adrenaline and compounds related to it raise the blood pressure. Clearly such differences may profoundly influence the therapeutic value of different compounds in different pathological conditions. Little therapeutic discrimination in this direction has so far been exercised. A serious claim has been made for veritol that its pressor action differs from most of the compounds under consideration. It has been extensively investigated by Rein (1937) and others. He finds that the pressor action comes on more gradually than that of adrenaline and lasts much longer, and is accompanied by little action on the heart. Constriction of the arterioles is regarded as being insufficient to explain the pressor action, which is ascribed mainly to a reduction in the amount of blood in the liver, spleen, and venous system. Favourable accounts have been published of its value in conditions of hypotension associated with vascular dilatation—for example, in bacterial infections, surgical shock, etc. I am not able here to enter into a detailed comparison of the possible therapeutic values of various compounds as pressor agents in different conditions. Those values have, in fact, not yet been adequately assessed. What is important is the fact that, if compounds differ in their relative actions upon the heart itself and upon different areas of the vascular bed, the therapeutic potentialities are increased, and further clinical experience may prove that some compounds may be more valuable than adrenaline not only from their more prolonged pressor action but because they have relatively more effect on the venous, or possibly capillary, channels than on the arterioles.

Cardiac Stimulation

Stimulation of the sympathetic nerve to the heart causes acceleration and augmentation of its contractions. Adrenaline produces conspicuously the same effects when perfused through an excised heart, though in the intact animal these effects may be masked by reflex slowing. The stimulus to the heart muscle given by adrenaline is

a powerful one. I found (Gunn, 1913) that when an isolated mammalian heart was perfused by a solution of chloral hydrate strong enough to arrest the heart in diastole, the addition of adrenaline to the chloral solution could restore the heart's contractions. In other words, adrenaline could antagonize a "fatal" degree of muscular depression of the heart produced by chloral. A similar antagonism was found to exist between adrenaline and chloroform or other heart depressants. Moreover, when an excised mammalian heart was kept in cold storage for over twenty-four hours and subsequent perfusion with oxygenated Locke's solution at blood temperature failed to initiate cardiac contractions, these began immediately when adrenaline was added to the perfusing solution. With Chavasse I found also (Gunn and Chavasse, 1913) that isolated rings of the cardiac portion of the superior vena cava, which showed no signs of spontaneous contraction, could be made to beat rhythmically on addition of adrenaline to the Locke's solution. Hering (1906) had previously shown that stimulation of the cardiac sympathetic nerve can cause the quiescent heart to beat again.

Such experiments suggested the possible value of adrenaline (a) as a stimulant to cardiac muscle depressed by drugs or other agents, and (b) (what is not necessarily the same thing) as an agent to restore rhythmic contractility to an arrested heart. In an attempt to estimate its value for such purposes Martin and I (1915) did experiments to determine whether it was efficacious in reviving a heart arrested by chloroform, and, after standardizing a method of doing massage and artificial respiration, found that when such measures alone failed they were frequently successful when combined with adrenaline. Some of the factors which seem to be important for success in resuscitation, when the heart is actually arrested, I have discussed previously in this *Journal* (Gunn, 1921).

The question arises whether any of the compounds related to adrenaline would be more suitable than adrenaline itself as cardiac stimulants either when the cardiac muscle is depressed or when the heart has actually ceased beating. Experimental evidence on this point is unfortunately meagre. Many of the compounds mentioned in the table included in the first lecture produce augmentation and acceleration of the isolated heart comparable in quality to the effects of adrenaline. Generally the onset is slower and the effect less intense but more enduring than that produced by adrenaline. We found (Epstein, Gunn, and Virden, 1932), for example, that the methoxy-phenyl-ethylamines produced a pronounced and prolonged stimulation of the isolated heart.

In the previous section dealing with the pressor actions of these compounds it has been pointed out that they differ in the ratios of their cardiac and vascular activities. Veritol is said to have little action on the heart. Hildebrandt and Mügge (1931) have urged a caution against use of ephedrine as a stimulant in collapse owing to its irregular and poisonous action on the heart. It seems probable that further pharmacological and therapeutical investigations may discover a better cardiac stimulant than any at present in use. Though no compound promises to be more effective than adrenaline in starting an arrested heart, adrenaline has its drawbacks. The sudden steep rise of pressure may throw too great a strain upon a weakened heart muscle. Its direct action is brief but (though this depends partly upon the dose) fulminating. It is reasonable to suppose that better results might be obtained with a compound which has more gradual and permanent but less intense action, both on the heart and on the vessels, than adrenaline. Possibly in resuscitating

the heart it might be an advantage to use adrenaline to start the contractions, and to follow this up with an intravenous injection of one of the compounds which have a more prolonged but less intense action. There is scope for further pharmacological and clinical investigations on this point.

Local Vasoconstriction

Adrenaline has been extensively used as a vasoconstrictor in conjunction with local anaesthetics. Probably the original reason for this was to limit haemorrhage, but the intense vasoconstriction produced by adrenaline performs other functions. By slowing down the local circulation it delays the absorption of the local anaesthetic and prolongs the anaesthesia. For example, Stockton, Pace, and Tainter (1931) found that, whereas a 1 per cent. solution of procaine alone produced local anaesthesia lasting seven minutes, the same solution containing adrenaline 1 in 100,000 produced anaesthesia lasting fifteen minutes, and with adrenaline 1 in 25,000 the anaesthesia was prolonged for 230 minutes. The delayed absorption of the local anaesthetic produced by the vasoconstricting action of adrenaline is believed to have two other effects. As the escape of the anaesthetic into the general circulation is delayed, a smaller amount of the anaesthetic is necessary to produce an equal amount of anaesthesia, and the toxicity of the anaesthetic is reduced because a longer time is given for its excretion in proportion to absorption.

One general disadvantage of adrenaline for this purpose is that it is so highly toxic if it should accidentally gain entrance to a vein. There may be a special disadvantage when it is used with cocaine. As a basis for comparison with compounds related to adrenaline, I suggested to Dr. Gurd that he might do a control experiment to see whether adrenaline lowered the subcutaneous toxicity of cocaine. He found, somewhat to our surprise, that, of a group of mice each of which received a dose of 0.15 gramme per kilogramme of cocaine, 33 per cent. died; of a group which received the same dose of cocaine plus 1 in 10,000 adrenaline, 100 per cent. died. The same quantities of adrenaline alone produced no lethal effects. It is well known that cocaine potentiates the pressor and other actions of adrenaline, and it may also potentiate the toxic action. It does not equally potentiate the action of other local anaesthetics. So far as cocaine specifically is concerned, it would seem rash to assume that a combination of cocaine and adrenaline is necessarily less toxic than cocaine alone. This may be true of certain dose combinations but not of all.

Various compounds related to adrenaline offer certain advantages over adrenaline for combination with local anaesthetics—for example, more prolonged vasoconstriction, less toxicity, absence of potentiation with cocaine, and greater stability so that they can be sterilized by boiling. Naturally, in so far as they are less active than adrenaline, they have to be used in higher concentrations. Among the substitutes used for this purpose are ephedrine, metasympatol, corbasil, and propadrine. A sufficient range of controlled comparative experiments has not yet been done to enable a decision to be made as to which is the best vasoconstrictor for use with particular local anaesthetics. It is an important practical problem which merits further investigation.

Ecbolic Action

In the previous lecture the pharmacological actions on the uterus of adrenaline and various other compounds were considered. Adrenaline was early suggested as a remedy for post-partum haemorrhage, and this was justifi-

able on the pharmacological evidence in so far as no exception was then known to the rule that adrenaline stimulated the pregnant uterus. When Gunn and Gunn (1914) found, however, that in both the rat and the guinea-pig the pregnant uterus, whether exsected or *in situ*, was powerfully relaxed by adrenaline, this at once raised the question whether the pregnant human uterus was relaxed by adrenaline, as in that case the administration of adrenaline for post-partum haemorrhage would do more harm than good. To get some evidence of the reaction of the human uterus I investigated (Gunn, 1914) the response of strips of the exsected human uterus and of the Fallopian tubes, and found that adrenaline produced contraction of both. Rübssamen and Kligermann (1912) had previously recorded the same result by similar methods, though I was unaware of their paper when I did my experiments.

Only scanty evidence is available of the action of adrenaline on the human uterus *in situ*. Bourne and Burn (1927) found that, in women during labour, adrenaline produced a slight relaxation of the uterus. As both Rübssamen and Kligermann and I had used unnecessarily high concentrations of adrenaline, I thought that possibly this difference in response between the exsected uterus and the uterus *in situ* might be due to the higher concentrations in the former case. I got Maclachlan to re-investigate this point, but he found that the lowest concentrations of adrenaline that produced any effect on the isolated human uterus caused contraction. At the moment this is difficult to reconcile with the opposite effect found by Bourne and Burn in the human uterus *in situ*. In any case adrenaline itself is not a very promising ecboic, because its action is transient (even if motor) and the accompanying rise of blood pressure would aggravate haemorrhage.

Some of the related compounds, however, produce a more prolonged contraction of the uterus with a coincident smaller rise of blood pressure, and they are, relatively to their action on the uterus, less toxic than adrenaline. Moreover, many of them have a far wider range of stimulation of the uterus in different species of animals and under different functional conditions than has adrenaline, and would presumably be more certain of stimulating the human uterus. Tyramine seems to be the only one which has been tried clinically, and with rather conflicting results. Actually there are other compounds more promising than tyramine on the pharmacological evidence, and it is not impossible that one of these may yet be found to be a satisfactory uterine stimulant in the human subject.

Action on the Bronchi

Since its introduction for this purpose adrenaline has been extensively used in spasmodic asthma to relax the bronchi. It is usually given hypodermically, and often small doses suffice. It is effective in a high proportion of cases and acts promptly. Administered hypodermically, it has little effect on blood pressure, but not infrequently causes palpitation or precordial distress and occasionally symptoms of collapse. The chief drawbacks to it are the brevity of its action and the fact that it must be given by injection. Up to the present time its most serious rival among the related compounds has been ephedrine, which has the merit of more prolonged action and of being effective by oral administration, a fact which is of especial value in the treatment of children. It is generally agreed, however, that ephedrine is less effective in a severe acute attack of asthma and that it is less certain in its action than adrenaline. It is often valuable as a prophylactic.

As a prophylactic in nocturnal asthma its value is diminished by its tendency to produce insomnia, due both to its pressor effect and to its stimulating action on the central nervous system. The ideal anti-asthmatic is not yet to hand, and theoretically it ought to be possible to find within this group of compounds one which could combine the merits of adrenaline and ephedrine with less of their disadvantages—for example, a compound which would be active by oral administration, have a more prolonged action than adrenaline and a more certain action than ephedrine, but be devoid of the latter's stimulant action on the central nervous system. Progress in this quest has been hampered by the difficulty of establishing reliable pharmacological methods of measuring bronchial reactions (difficulties which have been discussed by Handovsky (1935) and others), and also, from the clinical side, by the difficulty of assessing the value of a remedy in asthma, the attacks of which are so variable in onset and in which effects of suggestion, often temporarily effective, are sometimes only with difficulty eliminated.

As is perhaps to be expected from the experimental difficulties, there is much conflict of opinion in regard to the action of compounds on the bronchi. The effect of ephedrine varies considerably, according to the species of animal used as well as to the condition of the bronchi in a particular animal. This explains part of the discrepancy in the pharmacological results obtained with it. Ephedrine is believed to cause shrinkage of the nasal mucous membrane even when given by mouth, and it may have a similar effect on the bronchial mucous membrane, which would widen the lumen of the bronchi and might so alleviate certain cases of asthma.

As has been said, there is reason to hope that more reliable and satisfactory anti-asthmatics may yet be found within this group of compounds. Such claims have in fact been made for some of them, but these claims have as yet been scarcely sufficiently substantiated.

Stimulation of the Central Nervous System

It has already been shown that a stimulant action on the central nervous system, which is not exhibited by adrenaline, is conspicuously possessed by compounds which have an isopropylamine side-chain and which have the benzene ring of the nucleus either unsubstituted or with methoxy or methylenedioxy groups in the 3:4 position. To this series of compounds belong ephedrine and benzedrine. The stimulant action affects mainly the motor cortex and the respiratory centre. One therapeutic indication for such compounds is their possible value as antagonists to hypnotics and anaesthetics, for which their pressor action might be an additional asset. Such an antagonistic awakening action of ephedrine was early shown by Chen and Schmidt (1924) and others against hypnotics like chloral, and a stimulant action on the respiration was also observed in morphine poisoning. It was found that benzedrine is a more powerful stimulant than ephedrine, and estimations have been made of the relative efficiency of ephedrine and benzedrine compared with other well-known stimulants such as picrotoxin, cardiazol, coramine, and strychnine, in antagonizing overdoses of central depressants.

Various hypnotics, though they agree generally in depressing the central nervous system, differ considerably from one another in degree, duration, and site of action, and the analeptics mentioned above differ in these respects even more. Consequently it is not surprising to find that each analeptic has different antagonizing values to different depressants. Many investigations of this type of

antagonism made by a number of workers lead to the conclusion that the curative value of a particular analeptic varies with (a) the particular depressant used, (b) the dose of it, and (c) the species of animal employed (Hildebrandt, 1936). This being the case it is difficult to arrange analeptics in an order of merit that would apply generally to all depressants. Moreover, the variability in different species of animals urges caution in assuming that the results obtained especially in one species of laboratory mammals will be duplicated in man.

Barlow (1935) found in an extensive series of experiments that in rabbits poisoned with pentobarbital, chloral hydrate, and avertin the most successful stimulants were picROTOXIN, cardiazol, and ephedrine in that order. Chakravarti, quoted by Burn (1939a), similarly found that picROTOXIN and cardiazol could reduce the mortality of mice poisoned with nembutal, whereas benzedrine and ephedrine failed, though the latter were effective respiratory stimulants and, especially benzedrine, had a powerful awakening effect. Raginsky and Bourne (1931) showed that, both in dogs and in man, rectal anaesthesia with avertin could be interrupted or shortened by ephedrine. The data at present available from these and similar experiments are insufficient to assess the value of members of the adrenaline group as antidotes to narcotics. The pharmacological evidence rather suggests that they will be inferior to picROTOXIN or cardiazol; but possibly in cases of poisoning with narcotics in man the best results may be obtained by symptomatic treatment, if necessary with a combination of drugs, using those which especially stimulate the cortex, respiratory centre, or circulation, as these systems may seem individually to require them.

The stimulant action of these compounds has been used also in pathological states of nervous depression. This began with the employment, by Prinzmetal and Bloomberg (1935), of benzedrine in the treatment of narcolepsy. Solomon, Mitchell, and Prinzmetal (1937) found it useful in post-encephalitic Parkinsonism, where it produced a subjective feeling of increased energy, diminished tremor and rigidity, and frequently caused disappearance of oculogyric crises. Ephedrine they found far less effective. Davidoff and Reifstein (1937) gave a good résumé of the uses of benzedrine in depressive conditions and of various undesirable reactions that may occur with it. In the last few years many reports have been published of its therapeutic values and limitations in nervous diseases, including a recent one in this *Journal* (Anderson, 1938). The main result of these investigations has been to show that benzedrine is of some value in narcolepsy and Parkinsonism and in the milder types of depressive neuroses. Caution is urged against its use in cases of cardiovascular disease, and most authors emphasize that it should be given only under strict supervision.

At present it would seem that benzedrine may find a limited but not negligible field of usefulness in nervous diseases. As has previously been said, some of the related compounds seem to be even more powerful stimulants than benzedrine, with sites of action very similar to, but not absolutely identical with, those of benzedrine. Possibly one or other of these might be an improvement on benzedrine for the treatment of nervous depressions, but it is not reasonable to expect that they would have any much wider sphere of usefulness than that drug.

Action on Voluntary Muscle

Originally, as the result of an accidental observation, it was found that ephedrine produced an improvement of muscular activity in cases of myasthenia gravis, and it

has had a considerable use in this disease in recent years. While the effect was beyond dispute, it was unknown whether it was due to a central or to a peripheral action. The only evidence in support of the latter was the observation by Kreitmair that strong solutions of ephedrine produce a slight improvement in the contractions of the frog's gastrocnemius. An important contribution to this problem has quite recently been made by Burn and Bülbring (1939b), who have found that in a cat in which the sciatic nerve had been repeatedly stimulated until fatigue occurred an injection of ephedrine produced a large and prolonged rise of tension of the muscle. They found tyramine twice, and dihydroxyphenylethylamine twenty times, as strong as ephedrine, and suggest that these compounds should be tried in myasthenia gravis. The action of the latter substances is described as prolonged, which is rather surprising in view of their relatively brief actions on blood pressure. In a disease like myasthenia gravis duration of action is of almost more importance than intensity. In any case these experiments of Burn and Bülbring are not only explanatory but have suggested experimental avenues by which compounds superior to ephedrine in myasthenia gravis may be discovered.

Among other organs which these compounds have been used to influence therapeutically may be mentioned the bladder. The effect of sympathetic stimulation on the bladder varies somewhat in different animals, but the most general effect is relaxation of the detrusor muscle, with contraction of the sphincter and trigone. Such an action would lead to retention of urine, and gives an explanation of the beneficial effects from the use of ephedrine in the treatment of nocturnal enuresis in children. In this condition the wakefulness produced by ephedrine is a disadvantage. It can be mitigated by small doses of phenobarbitone (Brookfield, 1935), but it would seem possible that other compounds might be found to possess the same action on the bladder without the stimulant action of ephedrine on the central nervous system. This action of ephedrine, which is of therapeutic value in nocturnal incontinence, is often a drawback to the use of ephedrine in other conditions in which it may produce an unwanted difficulty in micturition.

Myerson and Ritvo (1936) observed that benzedrine orally administered produced relaxation of the smooth muscle of the gastro-intestinal tract, and greatly facilitated x-ray examination, making differential diagnosis between functional and organic spasm more certain. They found it useful in spastic colitis and pyloric spasm. The stomach emptied itself more rapidly under the influence of benzedrine owing to the relaxation of the pyloric sphincter. This action of benzedrine is rather surprising, as sympathetic stimulation in most animals produces contraction of the pyloric sphincter and relaxation of the fundus, and is in direct contrast to the action of ephedrine, which was found by van Liere, Lough, and Sleeth (1936) to delay the emptying of the stomach in man. In these circumstances it is difficult to predict whether any of the other compounds might be superior to benzedrine for relaxing gastro-intestinal spasm. The question would have to be decided by experiments in man.

Adrenaline has been recommended for the arrest of haemorrhage in gastric ulcer, from its local action in constricting the arterioles. Underhill and I (1914) found that, in contradistinction to its action on the main muscle of the gastro-intestinal canal, adrenaline constricted the muscularis mucosae, and we suggested that benefit resulting from adrenaline in gastric ulcer might be partly due to this action, which might aid in arresting capillary haemorrhage. The use of adrenaline itself in gastric ulcer

has not gained much acceptance, though some still claim beneficial effects from it if given in sufficiently large doses. None of the other compounds has, to my knowledge, been tried in this condition. It is conceivable that a compound less quickly destroyed than adrenaline and less likely to produce an after-dilatation of the vessels might be more successful in arresting gastric haemorrhage.

Conclusion

In this consideration of the therapeutic uses of adrenaline and of some compounds related to it, it has been possible only to indicate the wide range of potential values of members of this group, and even these indications are not exhaustive. There is scarcely an organ in the body which may not be influenced in one way or other by these compounds, and that not merely by general or local changes in the circulation: they affect not only smooth muscle in all organs but also the central nervous system and the voluntary muscles.

Pharmacological investigation has shown that, with slight changes in the chemical constitution, compounds can be found in which one pharmacological property can be increased and another diminished, whereby not only are the therapeutic possibilities increased but desirable actions can be enhanced and undesirable actions eliminated. Our knowledge of the therapeutic values of these compounds has by no means reached finality. Here and there suggestions have been made as to further explorations which may provide better remedies than those at present in use.

It need hardly be said that it has been possible in these lectures to refer only to a small part of the extensive literature on the subject. If undue emphasis has been laid on those aspects in which I have myself been interested, it is only because one object of the Oliver-Sharpey Lectures is to elicit personal experiences.

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THE CAUSATION OF DELAYED UNION AND NON-UNION OF FRACTURES*

BY

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The healing of a fractured bone is the outcome of several processes in which different tissues and fluids of the body bear their part. It is therefore certain that no single explanation can cover all cases of delayed union or non-union. Probably the most logical method of approaching the problem is to state briefly what takes place in the normal healing of a fractured bone and then consider the factors that may interfere with the desired result.

The Normal Healing of Bone

From a radiographic point of view, when a fracture has taken place the edges of the bones are clear-cut. Provided healing proceeds satisfactorily, in a few days the edges become less definite, presenting an eroded moth-eaten appearance. This erosion may be so great that the actual fracture line itself seems to increase considerably in width. At a later date, which in children may be as early as the tenth or twelfth day, ossified callus is seen to be laid down around the fracture site in the form of a plumber's wiped joint. At the same time it can be noted that the medullary cavity is entirely obliterated with new bone, both at the line of fracture and slightly above and below it. After a period, which may be months, the medullary cavity is re-formed, the excess callus is absorbed, and the cortex is restored to its normal shape and density.

From a histological point of view, when a fracture takes place the space between the fragments is filled with blood, and the neighbouring bone-cell spaces are occupied by bone cells. The periosteum is usually torn across and slightly stripped up from the bone at the edges of the fracture; and there is a tear into the soft tissues, which in the majority of cases include muscles. By the eighth or tenth day the space between the bones is filled with very elementary mesoblastic tissue, which is almost myxomatous at first and later takes the form of fibroblasts. This elementary mesoblastic tissue arises from the marrow cavity, from the Haversian canals, from the endosteum, from the periosteum, and from the mesoblastic tissue which forms the sheaths of the torn muscle bundles—in brief, from all tissues of mesoblastic origin in the area. Collagen fibres form in the exoplasm between the cells, and here also are seen minute blood vessels with walls a single cell thick. From the tenth day onwards calcium and other salts are deposited in the space between the cells. This deposition of salts is probably brought about by the action of the enzyme phosphatase, and it is to be noted that the optimum medium for the action of this enzyme is an alkaline one of pH 8.4. At a later date the mass of bone which fills the gap between the fracture ends, which fills the marrow cavity, and which forms the extra-cortical callus is absorbed or remoulded. The new lines assumed by the trabeculae are largely influenced by the stresses and strains put upon the bone.

From a chemical point of view, it is found that if fluid is aspirated from between the fragments on the first day it is largely composed of blood and has the same pH

* Read in opening a discussion in the Section of Orthopaedics and Fractures at the Annual Meeting of the British Medical Association, Aberdeen, 1939.