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

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LECTURE I: PHARMACOLOGICAL ACTIONS

Perhaps no single observation in physiology in the last half-century has had a more far-reaching effect on the progress of that science than the discovery by Oliver and Schäfer, in 1894, that an extract of suprarenal gland, injected intravenously, causes a swift and precipitate rise of blood pressure. The subsequent isolation and identification of the active principle responsible for this effect, the gradual elucidation of its manner of action, and, more recently, the discovery of its possible function as a transmitter of certain nervous impulses, have all played a fundamental part in the evolution of physiological and pharmacological concepts. The Oliver-Sharpey Lecture-ship was founded and endowed by George Oliver, with the expressed intention of "promoting physiological research by observation and experiment and encouraging the application of physiological knowledge to the prevention and cure of disease." He did this in memory of William Sharpey, of whom both he and Schäfer had been pupils in University College, London.

When I was honoured by the invitation to deliver these lectures I thought that it would be appropriate if I discussed some of the cognate work which has followed the pioneer researches of the founder of the lectureship himself, and I deem it all the greater privilege, in that I was myself a pupil of Oliver's colleague, Schäfer, who first aroused my interest in this subject.

By 1905 it was established that adrenaline has the structural formula

the final proof of the correctness of this formula being provided by the synthesis of the compound by Dakin and Stolz. Thus, within about a decade of the discovery of the pressor effect of the extract of suprarenal gland an active principle was isolated from the gland and its exact chemical constitution determined. Though before 1905 the existence of internal secretions of certain glands had been proved by circumstantial evidence, nothing was known in regard to the chemical composition of the active principles responsible for their physiological activities. The constitution of adrenaline showed that, in this case at any rate, the substance was of comparatively simple composition—less complex, for example, than that of most alkaloids. It was the first hormone to be synthesized, and there is no doubt that this rapid success with the chemistry of adrenaline gave an impetus and en-

couragement to the successful chemical study of other hormones.

The mystery attached to the internal secretions largely disappeared when adrenaline was shown to be a fairly simple body, capable of being manufactured in the laboratory, and the source of which, in the body itself, could at any rate be reasonably conjectured. It was also found that active principles more or less resembling adrenaline in structure and action—for example, tyramine and ephedrine—occurred in plants which have been used for medicinal purposes. This has been an important factor in dispelling the idea of the "unnaturalness" of drug treatment, because substances occur in medicinal plants or can be artificially synthesized which are closely related chemically to a substance which is manufactured in the animal body, and which there exerts effects indistinguishable from those which we usually associate with "drugs."

Method of Action of Adrenaline

The sudden and steep rise of pressure produced by adrenaline was correctly ascribed by Oliver and Schäfer mainly to contraction of the muscle of the arterioles. It was soon found that the smooth muscle of practically every organ was affected by adrenaline. Before that time substances which were known to affect smooth muscles peripherally generally affected them qualitatively in one direction. For example, barium or digitalis produced contraction of all smooth muscle, nitrites produced dilatation. Not unnaturally, therefore, the conception had arisen that any substance that acted on smooth muscle would act either as a universal stimulant or as a universal depressant of this tissue. Adrenaline, however, was different. It had a motor effect on the muscle of some organs—for example, the blood vessels, heart, or spleen—and inhibitor effects on others—for example, the intestine or bronchi. The actions of adrenaline on involuntary muscle seemed to admit of no "classification" according to either the structure or the function of the particular muscle. It seemed entirely arbitrary whether it would produce "stimulation" or "inhibition."

As the result of observations by many workers, notably Lewandowsky and Langley, a remarkable correspondence was shown to exist between the effects produced by stimulation of the post-ganglionic fibres of the sympathetic division of the autonomic nervous system and the actions of adrenaline. This correspondence was clinched by the extensive and definitive experiments of Elliott (1905), who showed that this correspondence held good over a wide range of organs and in many species of animals. An important generalization was now possible, and, though

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differences of opinion still existed as to the precise point at which adrenaline acted, the usual description given was that "adrenaline stimulated the termination of sympathetic nerves" and thus duplicated the effects produced when those nerves were otherwise stimulated—for example, by an electric current. Elliott, in fact, made the brilliant and daring suggestion that, in regard to the correspondence between the actions of adrenaline and sympathetic stimulation, the facts could be explained if it were supposed that a sympathetic nerve impulse acted on the muscle or gland not by a direct physical process but by the liberation, at the termination of the nerve, of a minute quantity of adrenaline. After a lapse of fifteen years the reality of this hypothesis was convincingly proved by Loewi. Evidence from several angles is consistent in suggesting that adrenaline acts on the muscle rather than on the nerve ends. Thus, Loewi and Navratil showed that ergotamine did not prevent the liberation of the accelerator substance when the cardiac sympathetic was stimulated, but it did prevent it from manifesting its action. It had previously been known that degeneration of the sympathetic nerve did not prevent adrenaline from exhibiting its effect. Euler (1938) has recently shown that adrenaline constricts the perfused vessels of the human placenta, which are believed to be free from any nerve supply, and he draws the apparently inevitable conclusion that adrenaline acts on the muscle cell itself. This still leaves the question unanswered as to why adrenaline, acting directly on the muscle, should cause muscle to contract in one case and relax in another.

Dale showed (1906a) that after a suitable dose of ergotoxine a dose of adrenaline which, previously to ergotoxine, had produced its usual pressor effect might now produce a fall of blood pressure. Similarly ergotoxine may "reverse" the action of adrenaline on an excised tissue—for example, the rabbit's uterus—converting a motor into an inhibitor response. As the most feasible explanation of this phenomenon Dale suggested that the vessels received mixed vasoconstrictor and vasodilator sympathetic fibres, both of which are stimulated by adrenaline; ergotoxine paralyzes preferentially the motor fibres and, after its action, adrenaline can stimulate only the inhibitor fibres, hence the reversed effect of adrenaline. This explanation of adrenaline reversal would seem to require modification now that both ergotoxine and adrenaline are believed to act on muscle rather than on nerve ends.

If the action of adrenaline is not on the actual nerve ends, the simplest assumption that can explain its actions seems to be, as Elliott suggested, that there exist myoneural junctions which are distinct from the actual muscle in their reception of chemical stimulants, and that, as Barger and Dale (1910) suggested, "the myoneural junctions concerned with inhibition are not identical, in their affinities for chemical substances, with those which are concerned with motor effects." According to this conception adrenaline acts on both inhibitory and motor myoneural junctions, and as sympathetic stimulation produces both these effects adrenaline and other compounds which act like it can be described as "sympathomimetic." When a compound produces only motor effects on smooth muscle this may mean either that it acts directly on muscle or that it acts preferentially on the motor myoneural junctions. Some of the facts are more readily explicable on the former hypothesis because tissues such as the mammalian intestine, which apparently have little or no motor sympathetic supply, and presumably, therefore, little or no motor myoneural junctions, are nevertheless powerfully stimulated by some compounds of this group.

Perhaps it has been too readily assumed that there is a complete change in the chemical structures of the nerve end, myoneural junction, and muscle. If the interactions between drug and tissue are chemical at all, the "receptor" in the tissue upon which the drug acts must be some definite chemical substance or grouping. Such a chemical substance may not be the exclusive possession of nerve end, myoneural junction, or muscle, but may occur in varying proportions or varying accessibilities in each. If this be the case, then the attempt to classify the actions of compounds related to adrenaline as acting exclusively on one or other of these tissues would break down, as in fact it has done. What mainly concerns us here is to what extent a particular compound deviates from adrenaline in its actions on smooth muscle.

Compounds to be Considered

Once the chemical structure of adrenaline had been revealed attempts were soon made to determine whether the molecule in its entirety was necessary for exerting the particular actions of adrenaline. Much of the ground was cleared by the pioneer work of Barger and Dale (1910), who investigated a large number of synthetic amines, more or less closely related to adrenaline in structure, with a view to determining whether they possessed the "sympathomimetic" actions of adrenaline and what was their relative potency compared with adrenaline itself. Many other investigators have occupied themselves with this problem, and something over two hundred compounds have been investigated having the basic carbon skeleton of adrenaline and differing from one another only in replacement of a hydrogen atom in some part of the molecule by such simple substitutions as an alkyl, hydroxyl, or halogen group. Obviously it would be impossible here to give even a bare mention of all of these.

In such a brief and partial survey as can only be possible here I propose to confine myself to a limited number of compounds (see table) and to certain pharmacological actions only. The selected compounds differ from phenylethylamine, which may be regarded as the basic substance, only in the substitution of hydroxyl, methoxyl, or methyl groups for hydrogen. In regard to the benzene ring only such substitutions are considered when they occur in the 3- or 4-positions—those positions in which the hydroxyl groups occur in adrenaline. Not all the known compounds are included in the table, but most of those mentioned have been used therapeutically. The method of schematic tabulation of the chemical formulae is that used by Gaddum (1939). As the chemical formula of each compound can be derived from the table, their commercial names have been given to facilitate references to their therapeutic uses. The order of substances is arranged on a definite plan. The first nine compounds, which include adrenaline, have a side-chain

—that is, they are derivatives of ethylamine; the remaining compounds have a side-chain

—that is, they are derivatives of isopropylamine. There are certain important pharmacological differences between

the phenylethylamine and phenylisopropylamine compounds, a description of which will be facilitated by this separation of the compounds into the two groups A and B. Group A are further arranged roughly in order of increasing nearness to the constitution of adrenaline, beginning with phenylethylamine and advancing from a compound with no phenolic hydroxyl group to compounds with one and then two such groups. A somewhat similar arrangement is followed in Group B, beginning with isopropylamine. Compounds 3, 15, and 16 are introduced to exemplify the effects of methylation of phenolic hydroxyl groups. In the table is given also (Column VI) the pressor activity of the substances compared with adrenaline, expressed as the reciprocal of the dose required to produce, under similar conditions, a rise of pressure equal to that produced by adrenaline; and (Column VII) the durations of the pressor action of a compound in a dose equipressor with that of adrenaline. These values must be regarded as only approximate, different workers frequently giving different values.

Pressor Activity, Adrenaline = 1	Pressor Duration, Adrenaline = 1
A	1. β -phenylethylamine (PE)	H	H	H	H	1/200-1/80	3-4
	2. Tyramine	OH	H	H	H	1/100-1/20	2
	3. <i>p</i> -methoxy-PE	OCH ₃	H	H	H	1/300	4
	4. Sympatol	OH	H	OH	H	CH ₃ 1/100-1/25	4
	5. Metasympatol	H	OH	OH	H	CH ₃ 1/5	2
	6. Dihydroxy-PE	OH	OH	H	H	H 1/35	1
	7. Epinine	OH	OH	H	H	CH ₃ 1/12	2
	8. Arterenol	OH	OH	OH	H	H 3/2	2
	9. Adrenaline	OH	OH	OH	H	CH ₃ 1	1
B	10. Benzedrine-- β -phenylisopropylamine (PI)	H	H	H	CH ₃ H	1/300-1/100	5-10
	11. Propadrine	H	H	OH	CH ₃ H	1/300-1/60	7
	12. Ephedrine	H	H	OH	CH ₃ CH ₃	1/300-1/100	7
	13. Veritol	OH	H	H	CH ₃ CH ₃	1/30	10
	14. Corbasil	OH	OH	OH	CH ₃ H	1/4	2
	15. 3-methoxy : 4-hydroxy-PI	OH	OCH ₃	H	CH ₃ H	1/200	5
	16. Methyleneedioxy-PI		H	CH ₃	H	1/400	10
	I	II	III	IV	V	VI	VII

The basic substance of this group is phenylethylamine (Compound 1), from which adrenaline (Compound 9) differs in possessing (a) a phenolic hydroxyl in the 4 (para) position (I), (b) a phenolic hydroxyl in the 3 (meta) position (II), (c) an alcoholic hydroxyl in the beta position (III), and (d) partial methylation of the amino group (V). Consideration will be confined mainly to the effect on pharmacological action of two factors in chemical constitution: (1) free phenolic hydroxyl groups (I and II), and (2) methylation of the α carbon atom (IV).

Pressor Actions

INFLUENCE OF FREE PHENOLIC HYDROXY GROUPS ON INTENSITY AND DURATION OF PRESSOR ACTION

Barger and Dale found that *p*-hydroxyphenylethylamine (tyramine) has three to five times the pressor activity of phenylethylamine. The effect, however, lasts only about

half as long. Dihydroxyphenylethylamine (Compound 6) has a pressor activity probably slightly greater than that of tyramine, but the duration of action is again halved. In other words, with an ethylamine side-chain the result of adding phenolic hydroxy groups is to increase intensity but diminish duration of pressor action. A general survey of the compounds also discloses the fact that, with varying side-chains, the dihydroxy compounds (6, 7, 8, 9, 14) are distinguished by intense but brief pressor action.

What difference, if any, does it make if a single hydroxyl group is in the para or the meta position? Barger and Dale found that, with an ethylamine side-chain, the meta and para hydroxy compounds had about equal activity, but Tainter (1932) found that, with a side-chain corresponding to adrenaline, the meta compound (Compound 5) had definitely a more intense but less enduring effect than the para compound (Compound 4). The fact that the effect of a particular substitution may vary with other alterations in the molecule is not an unusual result and makes generalization hazardous outside the particular compounds studied. Nevertheless, from the data given above and from other evidence, it can be concluded that in this series of compounds the probable effect of adding a single hydroxyl group is to increase the intensity and diminish the duration of pressor action, and that these properties are especially manifested if the hydroxyl group is in the meta position, and are still further accentuated if two hydroxyl groups are added in these positions.

One reason, though possibly not the sole reason, for the diminished duration of action resulting from addition of phenolic hydroxyl groups is that this addition makes the compounds less stable—dihydroxy compounds, for example, deteriorating much more rapidly on exposure to light and air or on boiling than similar compounds lacking these groups. One method of rendering such compounds more stable is to methylate the hydroxyl group, and some years ago I got made four compounds—para and meta methoxy-, methylenedioxy-, and dimethoxy-phenylethylamines—in the hope that while they might retain some of the intensity of pressor action of the corresponding hydroxy compounds they would exert a more prolonged action. Actually the first three (for example, Compound 3) were found to have the anticipated more prolonged but less intense action than tyramine. On the other hand, the dimethoxy compound, which I expected to be the most active as having methoxyl groups in the same position as the hydroxyl groups in adrenaline, had only a very feeble pressor activity (Epstein, Gunn, and Virden, 1932).

All these compounds (1-9) have ($-\text{CH}_2-$) in the α position in the side-chain (IV). When the structure of ephedrine, a natural alkaloid occurring in certain species of *Ephedra*, was elucidated, it was found to resemble adrenaline fairly closely in structure, differing from it in the possession of a methyl group in the α position and in the absence of phenolic hydroxyl groups. Since its constitution was discovered many other compounds having the α methyl group have been synthesized and investigated, among which are Compounds 10-16.

It can be seen from the table that one effect of the α methyl group is to prolong the duration of the pressor effect, though the intensity is, if anything, diminished. Thus the basic phenylisopropylamine (Compound 10) (benzedrine) has a pressor activity less than phenylethylamine (Compound 1), but the effect lasts twice as long, and Compounds 10-13 all have a relatively prolonged action. One probable reason for those differences in duration of action is the relative ease with which different

compounds are destroyed in the body. Adrenaline is destroyed in the body by an amine oxidase which produces an oxidative deamination of the side-chain (Richter, 1937). By this means adrenaline can be rapidly inactivated, and but for some such mechanism to ensure this rapid inactivation it could scarcely fulfil its possible role as a transmitter of sympathetic nerve impulses. Blaschko, Richter, and Schlossmann (1937) have recently shown that the same oxidase deaminates also phenylethylamine, tyramine, sympatol, and epinine, but has no such action on benzedrine, ephedrine, or corbasil. In other words, it does not oxidize those compounds which have a methyl group in the α position. This affords a reasonable explanation of why the latter compounds produce a more enduring effect, as they will be less readily destroyed in the body; and it also possibly explains the fact that, of all these compounds, those which are especially effective when given by mouth are those having an α methyl group.

When the compound has two phenolic hydroxyl groups and also an α methyl group (Compound 14), the former again increase intensity but diminish duration (compare Compound 14 with Compound 11).

Actions on the Central Nervous System

In contradistinction to its remarkable activity on so many other organs, adrenaline has little action on the central nervous system. Even with fatal doses of adrenaline animals show no symptoms suggesting any important direct effect on the central nervous system, and especially no exaggerated excitability. Bry (1914) found that phenylethylamine produced a marked increase in the respiration rate and short-lasting convulsions, and it was later found that ephedrine, and especially benzedrine, produced a more pronounced stimulation of the central nervous system. In the last few years benzedrine has gained some reputation as a remedy in depressed conditions of the central nervous system and some notoriety as a "brain stimulant" outside medical practice. This has aroused more interest in the central actions of the whole group, and though many of the compounds have not been adequately investigated in this connexion, already certain points seem clear, enabling central stimulation to be correlated with chemical constitution. Some of the more significant findings may be briefly discussed here, and from two aspects: (a) changes in the benzene nucleus, and (b) changes in the side-chain.

(a) The stimulant action exhibited by phenylethylamine is almost lost in tyramine, and is even less manifest in compounds with two phenolic hydroxyl groups (Compounds 7 and 9). Alles (1933) found that, with an isopropylamine side-chain, the presence of one or two phenolic hydroxyl groups reduced the stimulant action of benzedrine. Epstein, Gunn, and Virden (1932) found that, with an ethylamine side-chain, the stimulant action manifested by phenylethylamine and disappearing with tyramine was restored in para and meta methoxy- and methylenedioxy-phenylethylamine but was reduced again in the dimethoxy compound. Hjort (1934), investigating a series of diphenylethylamines, later found that here also "the unsubstituted methoxy and methylenedioxy compounds are invariably excitants and convulsants. The hydroxy substituted members are depressants." There is sufficient unanimity on this point to enable one to say that, so far as the nucleus is concerned, central stimulation of the nervous system is likely to be found in compounds with unsubstituted, methoxy, or methylenedioxy groups and is likely to be absent in compounds with one or two phenolic hydroxyl groups.

(b) Alles (1933) found that phenylisopropylamine (benzedrine) is a more powerful stimulant than phenylethylamine, indicating that the isopropylamine is more stimulating than the ethylamine side-chain. Chen and Schmidt (1924) stated that rabbits narcotized by chloral could be easily roused by ephedrine, and that in morphine poisoning it stimulated the respiratory centre. Prinzmetal and Bloomberg (1935) found benzedrine more effective than ephedrine in the treatment of narcolepsy. Gunn, Gurd, and Sachs (1939) showed that methylenedioxy-phenylisopropylamine is more stimulant than methylenedioxy-phenylethylamine, and Gurd and I have found more recently that with a cyclohexyl nucleus the isopropylamine compound is again more stimulating than the ethylamine one.

With different types of nucleus, therefore, the addition of an α methyl group confers an increased stimulating property, provided the compound has no free hydroxyl groups. When two of the latter are present (Compound 14) their depressant effect overshadows even the stimulant property of the propylamine side-chain.

Combining (a) and (b) above, we can therefore, at least as a working hypothesis, assume that the most powerful central stimulants will be found in compounds with an unsubstituted, methoxy, or methylenedioxy ring and an isopropylamine side-chain. Acting on this hypothesis, Gunn, Gurd, and Sachs investigated methylenedioxy-phenylisopropylamine (Compound 16) and found that in mice and rabbits it had stimulant properties very like those of benzedrine, from which it differs only in possessing a methylenedioxy group. Under certain circumstances it seemed to be an even more powerful stimulant than benzedrine.

The characteristic stimulation of the central nervous system produced by such compounds is shown by marked acceleration of respiration and a great increase in co-ordinated motor excitability. Animals show, especially with large doses, abnormally rapid and frequent voluntary movements, such as one would expect from a stimulation of the motor cortex. Gurd and I (in unpublished experiments) have recently investigated a new type of compound with a cyclohexenyl nucleus which possesses this action to a remarkable degree. Under its influence mice, especially if several of them are together, dart from side to side of the cage with abnormal speed, knocking one another over, biting and squealing, and displaying a type of motor excitement which is scarcely equalled by benzedrine.

Toxicity

So far no mention has been made of the comparative toxicity of the compounds which have been considered, though naturally this is a question of the first importance. As toxicity differs in different species of animals and varies with the channel of administration, it is difficult to make accurate generalizations. One or two factors which influence toxicity may, however, be mentioned.

Tyramine is much less toxic than phenylethylamine or methoxy-phenylethylamine, and there is a good deal of evidence to show that the presence of a single phenolic hydroxyl group has a pronounced effect in reducing toxicity. Compounds with two such groups are generally more toxic than those with one. Thus adrenaline is at least twenty times as toxic as metasympatol. Adrenaline is in fact the most toxic of all, and this must be partly due to the alcoholic hydroxyl group, for it is very much more toxic than epinine.

Acting on the conclusions previously mentioned in regard to the modifications in intensity and duration of

pressor activity, central stimulant action, and toxicity produced by the introduction of certain groups in the molecule of phenylethylamine, an attempt was made to design a compound with certain definite properties (Compound 15)—namely, a compound which would be more stable and have a more prolonged action than adrenaline or tyramine, but lack the central stimulant action of benzedrine or ephedrine, which is sometimes a disadvantage—for example, from the consequent insomnia. To increase stability and duration of action a methoxyl group was introduced into the nucleus and an α methyl group into the side-chain. To diminish toxicity and central stimulation a para-hydroxyl group was added. The substance was synthesized by Sir Robert Robinson. Actually it was found to have most of the anticipated properties. It had only one-sixth of the toxicity of benzedrine and practically none of the latter's central stimulating action; so that the phenolic hydroxyl group had successfully combated the toxic and stimulant effects of methyl and methoxyl groups. Its pressor effect lasted about five times as long as that of adrenaline and two and a half times that of tyramine, and only slightly less than that of ephedrine. It was, however, only about half as toxic as ephedrine. These results apply only to laboratory animals, and sufficient evidence is not yet at hand to decide whether this compound will display these qualities equally in man. In any case, however, the compound shows that, in a homologous series of drugs, one can, as the result of previous experience, predict the effect of changes in constitution with a reasonable prospect of success.

Actions on Involuntary Muscle other than Cardiovascular

Most workers, following Barger and Dale, have endeavoured to determine whether the compounds they used were sympathomimetic or not, and it has been found that few compounds reproduce the effects of sympathetic stimulation with the completeness and fidelity that are shown by adrenaline. On the other hand, nearly all amines, ranging in constitution between phenylethylamine and adrenaline, agree in exhibiting an action on smooth muscle in relatively low concentrations, regardless of how they may differ otherwise in action—a fact that may be of some biological significance. Barger and Dale found different ratios of motor and inhibitor activity with different compounds, and other workers, using still other compounds, have obtained similar results. If the compounds related to adrenaline could in this connexion be classified into two divisions—(a) those which, like adrenaline, are strictly sympathomimetic, and (b) those which stimulate all smooth muscle—the problems as to pharmacological classification and therapeutic indications would be simplified; but a survey of these compounds reveals that they do not fall into so simple a classification.

The divergent actions of these compounds can conveniently be illustrated by their effects on the uterus, partly because this organ has been extensively used as a test object of sympathomimetic action. Here not only do the uteri of different species of animals respond differently to adrenaline, but the responses given by compounds related to adrenaline may differ from those given by adrenaline itself. It was shown by Langley (1901) that the uterus of the rabbit reacts to adrenaline by a motor effect whether the uterus was pregnant or non-pregnant. On the other hand, it was shown independently by Cushny (1906), Dale (1906b), and Kehrer (1906) that in the cat, while the pregnant uterus responds, as in the rabbit, by contraction, the non-pregnant uterus is relaxed

by adrenaline. Gunn and Gunn (1914) found still another type of innervation in the rat and guinea-pig, for in these animals the uterus is inhibited by adrenaline in both the pregnant and the non-pregnant condition. A comparison of the effects of a compound on the uteri of these animals affords one convenient method of determining whether the compound acts sympathomimetically or directly on the muscle.

Epstein, Gunn, and Virden (1932) found that the para- and meta-methoxy- and methylenedioxy-phenylethylamines inhibited the non-pregnant uterus of the cat like adrenaline, but, unlike adrenaline, contracted the uteri of the rat and guinea-pig. From these and other experiments they concluded that these compounds acted sympathomimetically in cats but not in rodents. Gunn, Gurd, and Sachs (1939) found that phenylisopropylamine and some related compounds produce contractions of the uterus in all animals, including the non-pregnant cat. So far as the uterus is concerned, therefore, these compounds fall into at least three groups: (a) those which, like adrenaline, are strictly sympathomimetic; (b) those which are sympathomimetic in one species of animal but not in another; and (c) those which stimulate uterine muscle universally and with no relation to the quality of sympathetic stimulation. Other workers have found somewhat similar results with other compounds.

If the effect of sympathetic stimulation is to make a muscle contract, then it is from the therapeutic point of view perhaps immaterial whether a compound is sympathomimetic or whether it stimulates muscle directly. If, on the other hand, sympathomimetic stimulation makes a muscle relax, a sympathomimetic compound will have the opposite effect to one which stimulates muscle directly. It is therefore not surprising that much experimentation has been directed to determine whether a compound produces, on smooth muscle in certain organs, those dilator effects that are characteristic of the actions of adrenaline. This is especially important in the search for remedies against asthma. Of the work done in this connexion it is difficult to make any generalizations to which exceptions cannot be found, but one or two points may be mentioned. Barger and Dale concluded, from a study of the compounds available to them, that "of the catechol bases those with a methylamine group, including adrenaline, reproduce inhibitor sympathetic effects more powerfully than motor effects." For example, adrenaline and epinine produce these inhibitor effects better than arterenol. Similarly, ephedrine shows those actions better than benzedrine, which differs from the former in the lack of the methylamino group. In some other compounds, however, the presence of this group seems to be of less importance in conferring inhibitor properties. Another factor which conduces to this inhibitor action is the presence of two hydroxyl groups in the 3:4-positions, but inhibitor properties more limited in degree or extent are found in compounds—for example, ephedrine or tyramine—which lack these groups.

Summary

Even this necessarily superficial and partial survey of the pharmacological actions of some compounds related to adrenaline may give an indication of the possible value of investigations in this field. So far as the problem of relating chemical constitution to pharmacological action is concerned, this group of compounds is an interesting one, partly from its general biological interest as being related to an important hormone and partly because the basic molecule is not too complex, so that such

relations, if they exist, can be more readily established. One action which is retained by compounds based on phenylethylamine, in spite of considerable changes in the molecule, is an action on smooth muscle.

In some cases this can be described as a sympathomimetic action, in others as a direct action on muscle, in others as a mixture of these actions. In virtue of these actions they affect all organs containing smooth muscle—heart, blood vessels, bronchi, intestinal canal, uterus, spleen, etc. They have thus a wide range of activity with potential therapeutic uses. Some of them also stimulate the central nervous system, especially the motor cortex and the respiratory centre. Some examples have been given of how the molecule can be altered to diminish or intensify the various effects of the resulting compounds. The assessment of their therapeutic values, usually a slow process, probably lags behind the pharmacological knowledge we already possess, but some consideration of such therapeutic progress as has been made will be given in the second lecture.

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(The second of the two lectures will appear next week.)

The National Institute of Industrial Psychology (Aldwych House, London, W.C.2) has issued a report on rest-pauses and refreshments in factories. The results are based on information obtained by personal interviews with responsible officials in 1,050 factories, employing about 305,000 workpeople. Equal numbers of factories were visited in seven industrial areas of Great Britain. A wide variety of industries was included, though such non-factory activities as mining, building, transport, shipbuilding, the distributive trades, and offices were omitted. The object of the inquiry was to record the facts of existing practice, and to discuss the views of those who contributed to the inquiry. It was found that 52.9 per cent. of the factories visited made provision for official rest-pauses, either in the morning or afternoon. More than half of the factories visited which have rest-pauses have introduced them during the past decade. In practically all instances official rest-pauses were spent in taking refreshments. Of those employers who gave information relative to the effects of rest-pauses on efficiency 82 per cent. considered that the effects were good, while only 3.4 per cent. regarded the results as unfavourable. Although the primary object of rest-pauses is to reduce fatigue and nervous strain, it appeared that other reasons influenced employers more when introducing rest-pauses. The most important of these reasons were the need of refreshments by those, especially young girls, who had inadequate breakfasts; Factory Act requirements; and the desirability of regularizing unofficial rest-pauses which employers had found to be unsatisfactory.

THE ELECTRO-ENCEPHALOGRAM AS AN AID IN CLINICAL NEUROLOGY

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It has long been known that nervous activity is accompanied by changes of electrical potential. In 1929 Berger, employing thermionic amplification, was able to record from the intact cranium rhythmical electrical changes which he claimed were produced in the cerebral cortex. It was not until 1934, when Adrian and Matthews confirmed this work and introduced important refinements into the technique, that the ground was prepared for further research into the electrical activity of the brain. Since then a considerable amount of experimental work has been done on the action potentials of the exposed cortex of animals. Grey Walter (1936, 1937), employing a modification of the method devised by Adrian and Matthews, studied the electrical changes associated with pathological states of the human brain, and his work in this field has already attained considerable importance.

Evidence exists that numerous electrical rhythms or discharges arise from various areas of the brain and that the type and nature of these rhythms are in some way related to variations in the cyto-architecture. It is not surprising to find, after all the investigations into the electrical nature or accompaniment of the propagation of nervous impulses, that the cell stations in the central nervous system responsible for these impulses do themselves show evidence of electrical flux. It would appear that within the central nervous system there are an infinite number of potential changes—as many changes as there are active neurones; but it is only when certain groups of units, because of a common cyto-architecture, or because of like activity in the physiological sense, act in unison or “beat” together that it is possible to pick up characteristic changes on the surface of the exposed brain. Further complications arise when the electrical changes are studied with the overlying structures intact—that is to say, cerebrospinal fluid, meninges, bone, and superficial tissues. These act as a number of resistances of different values linked in parallel and common to all intracranial electrical events. The effect of the overlying structures is to reduce very considerably the magnitude of the electrical changes which occur—so much so that isolated groups of changes can no longer be picked up, and only the results of mass or “beat” action of a group of events can be detected. The issue is still further complicated because these overlying structures either exhibit or conduct further bio-electric changes—eye movements and action potentials from muscles, such as the temporal muscle, being the most obtrusive. A factor to which too little attention seems to have been paid by some workers in this field is the “noise-signal” ratio of the amplifiers themselves. One sees many records published in which much of what is assumed to be brain activity is in reality a summation of background noise and other unwanted potential changes, with nothing more than an “overlay” of the actual changes. Many of the undesirable effects occur at relatively high frequencies and can be reduced to negligible proportions by the incorporation of suitable filter circuits. These