A NEW VASODILATING PHARMACEUTIC

by H. D. MOED *).

In vascular disorders like arteriosclerosis, vital functions of the human organism are endangered because the blood is unable to circulate freely through certain parts of the body. There is accordingly a demand from the medical side for a drug that is capable of restoring freedom of circulation where this has been impaired. This has given impetus to a whole series of investigations in various countries; in the Philips research laboratories, Netherlands, it has led to the development of “Duvadilan” **), which has quickly been adopted for large-scale medical employment as a vasodilating and spasmolytic agent. The following article seeks to give an account of these investigations, which may be regarded as being of pharmacological and chemical as well as medical interest.

Introduction

The body contains a great variety of substances that influence the activity of organs and other functional systems. It is one of the functions of the pharmacologist to ascertain the actions of such substances and the mechanisms underlying their effects. A common procedure in pharmacological research is to modify the molecule of the active substance in various ways and to investigate the associated changes in its pharmacological properties. This knowledge may be of value when a drug with a given action is being sought. Investigations of this kind, carried out on adrenaline, have yielded results that have an important bearing on the treatment of certain vascular disorders such as arteriosclerosis in the head and limbs, and Bürger’s and Raynaud’s diseases.

Adrenaline is a hormone secreted by the adrenal gland and possesses a particularly complex set of actions in the body, to which we will start by devoting some attention.

1) Adrenaline has an effect on the blood-vessels, dilating the vessels in certain kinds of tissue (skeletal muscle, for example) and constricting those in other kinds (the skin and the intestines).

2) It also affects the heart, causing tachycardia (speeding up the heart rate) and strengthening the contractions.

3) It has a relaxant effect on the smooth musculature of the bronchial passages and of the intestine.

4) It plays a part in sugar metabolism, the effect being to raise the concentration of sugar in the blood.

A certain pattern can be seen in these many effects if adrenaline is regarded as the hormone that makes the body capable of sudden great exertion. Adrenaline has in fact been called the “escape hormone”. The skeletal muscles used in a fast escape require an extra generous supply of blood; hence the dilation of their blood-vessels and the reinforcement of heart action. Other parts of the body that are of secondary importance for the time being have to make do with a smaller supply; hence the vasoconstriction in the region round the intestine and the relaxation of muscles in the intestinal wall. Dilation of the bronchial passages, resulting in increased oxygen uptake, is another desideratum for flight.

Important as it may be for self-preservation in man and animals, the mere fact of this complex set of actions, together with the difficulty of controlling them properly, means that adrenaline is not entirely suitable for therapeutic purposes. Its vasodilatory effect could be very useful in the treatment of the diseases named above, in which the free circulation of the blood is impeded by the spastic state of the vessels, for example, or by thickening of their walls; but the accompanying effects on the heart (palpitation) would be troublesome and sometimes even harmful. Another disadvantage is that adrenaline is ineffective when given orally.

*) N.V. Philips-Duphar, Weesp, Netherlands.
**) Registered trade-mark by N.V. Philips-Duphar and sold under this trade-mark in most countries. In some countries “Duvadilan” is sold under a different trade-mark, e.g. “Vasodilan”, “Dilavase” and “Cardilan”.

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Extensive research at the Central Laboratory of N.V. Philips-Duphar, Weesp (Netherlands), has resulted in the synthesis of isoxsuprine (*), a derivative of adrenaline which is marketed under the name of “Duvadilan”. This preparation has proved to be a particularly useful one in that it induces marked vasodilation when given orally (or by other routes) while having little effect on the heart. It is accordingly of considerable value in medicine.

In the section which follows, the actions and molecular structures of adrenaline and isoxsuprine will be compared with those of some other adrenaline derivatives in order to show more clearly the specific properties of isoxsuprine. Attention will then be given to the synthesis of the drug, and to the mechanism of the relevant chemical reaction. Finally, clinical data and the results of animal experiments will be given to illustrate the pharmacological actions of isoxsuprine.

**Adrenaline derivatives**

**Relationships between adrenaline, noradrenaline and the sympathetic nervous system**

As we have learned from the above, one sometimes wants to retain one effect of a substance while eliminating another. The belief that this is possible implies the assumption that each of the given effects is the result of action on an appropriate receptor, and that the structural elements of the substance essential for its action on one kind of receptor are different from those essential for its action on another kind. Receptors can be thought of as regions of tissue with a specialized structure on which the drug takes hold. There is experimental evidence in support of the idea that different kinds of receptors exist, and that they work independently. Firstly, altering the chemical structure of a substance may modify its individual effects in different ways. Secondly, it is possible for some of the effects to be suppressed by a second substance, the other effects persisting. Convincing evidence of the first kind can be obtained by comparing the effects of adrenaline with those of noradrenaline and isopropylnoradrenaline, which are substances chemically related to adrenaline and are classed as sympathomimetic (this term will be explained later). Noradrenaline is another hormone secreted by the adrenal gland, and isopropylnoradrenaline is a compound derived from it. The effects of these three compounds are compared in Table I; from this it is clear that noradrenaline only partly shares the effects of adrenaline, and that isopropyl-

<table>
<thead>
<tr>
<th>Effect</th>
<th>noradrenaline</th>
<th>adrenaline</th>
<th>isopropyl-noradrenaline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasodilation (skeletal muscles)</td>
<td>0</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Vasoconstriction (skin, intestines)</td>
<td>+</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Bronchodilation</td>
<td>0</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>0</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

noradrenaline produces precisely those effects of adrenaline which are not shared by noradrenaline. On the basis of such observations Ahlquist 1) postulated the existence of two types of sympathomimetic receptors which he called α and β.

In order to understand the meaning of the name “sympathomimetic”, let us look into the links between adrenaline, noradrenaline and the function of the nervous system. A number of vital functions, including metabolism and blood flow, are to some extent under the control of the autonomic nervous system. It is a dual form of control exercised by the two parts, sympathetic and parasympathetic, into which the autonomic system can be divided. In general, stimulation of the sympathetic system results in enhanced activity, whereas stimulation of the parasympathetic system results in relaxation and recuperation.

In both these systems stimuli are transmitted from nerve cell to nerve cell and finally from nerve cell to tissue by means of chemical substances. In both it is acetylcholine that passes on the stimulus from one nerve cell to the next, and in the parasympathetic nervous system the same chemical is responsible for transmission to the tissues; but in the sympathetic system this latter responsibility is reserved for noradrenaline and, in a lesser degree, for adrenaline.

Substances whose action on the tissues produce effects like those of stimulation via the autonomic nervous system are classed as “sympathomimetic” or “parasympathomimetic”, depending on the stimulated systems (“-mimetic” meaning “mimicking”). The opposite categories of “sympatholytic” and “parasympatholytic” include substances with the

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(*) Generic name registered at the World Health Organization.

ability of suppressing the effects in question ("α-lytic" meaning "loosing" or "releasing from").

Let us now return to the postulation of Ahlquist regarding the existence of two types of sympathomimetic receptors. Vasooconstriction in the skin is thought to be the result of sympathomimetic substances acting on the α-receptors and is therefore classed as α-sympathomimetic; β-sympathomimetic effects include vasodilation in skeletal muscles and dilation of the bronchial tubes. Noradrenaline is believed to act on α-receptors only, adrenaline on both types, and isopropylnoradrenaline on β-receptors only.

For brevity, we shall refer to the above as α-mimetic and β-mimetic substances. The terms "α-lytic" and "β-lytic" are also used with reference to the opposite categories — see above. The theory is that these lytic substances attach themselves to α-receptors or β-receptors without giving rise to the appropriate effect; by engaging with or occupying the receptors, it is thought, they prevent adrenaline and noradrenaline exercising their particular sympathomimetic effects.

Now that this background has been sketched in, it can be seen that a big advance will have been made in the direction of a "specific" vasodilating agent if a substance can be produced which combines a β-mimetic with an α-lytic action. The line followed in our investigations will be easier to understand if this is kept in mind. Other factors that had an important bearing on these investigations are mentioned in the next section, in which the structure of isoxsuprine is described.

The chemical structure of isoxsuprine as compared with the structures of adrenaline, noradrenaline and other related substances

Fig. 1 shows the structural formulae of adrenaline, noradrenaline, isoxsuprine and ephedrine. As can be seen, they all contain the group

\[
\text{OH} \quad \text{C} \quad \text{H} \quad \text{C} \quad \text{N} \quad \text{CH}_3
\]

This group appears to be essential if a sympathomimetic effect is to be obtained. In this connection ephedrine (fig. 1) is of some interest. This is a naturally occurring alkaloid prepared from the herb known to the Chinese as Ma Huang. In 1923 Chen and Schmidt \(^2\) showed that ephedrine has much the same properties as adrenaline. But there is an important difference: adrenaline is readily broken down, and for that reason is ineffective when given orally, whereas ephedrine is relatively free from this disadvantage. This is probably due to two things, the first being the methyl group which has been substituted on to carbon atom β (see fig. 1) and which serves in some degree to protect the neighbouring nitrogen from enzymatic action (which is one of the ways to breakdown the molecule). Secondly, the elimination of hydroxyl groups attached to the benzene nucleus also reduces the risk of breakdown, though in a different way. At the same time, unfortunately, the loss of hydroxyl groups greatly reduces the sympathomimetic activity of the molecule.

![Fig. 1. The structural formulae of adrenaline, noradrenaline, isoxsuprine and ephedrine.](image)

Mention has already been made of the striking differences which exist between the effects of adrenaline, noradrenaline and isopropylnoradrenaline. These differences indicate that the group to be substituted on to the nitrogen atom has an important influence on the sympathomimetic activity of the resulting compound. The question has been carefully investigated in experiments in which the methyl group in the adrenaline molecule was replaced by various other alkyl groups. In general this was found to result in a decrease in α-mimetic potency without any loss of β-mimetic action. In some cases there was even reversal of the α-mimetic action to an α-lytic one. In these investigations \(^3\) the compound that attracted the most attention was the previously mentioned isopropylnoradrenaline. This compound


\(^3\) H. Konzett, Arch. exper. Pathol. 197, 41, 1940/41.
has a bronchodilating effect three times as great as that of adrenaline. It is also a potent vasodilator. It is entirely free from the \(\alpha\)-mimetic effects of adrenaline on the nerve cells, but still has the undesirable effect of stimulating the heart, particularly when given orally. It affects the heart to a much less extent when inhaled and in this form it is very useful for relieving asthma.

The search for other groups suitable for attachment to the nitrogen was influenced by the thought that it might be possible to derive a substance which would relax vascular spasm in virtue of properties other than and additional to \(\beta\)-mimetic activity. Külz was the first to substitute phenylalkyl groups on to the nitrogen. Fig. 2 shows the chemical structure of the substance synthesized by Külz, together with that of papaverine. The latter is a spasmolytic drug possessing a direct action on muscle. Although Külz states that he was interested in a spasmolytic action, it is not certain that the analogy with papaverine was uppermost in his mind. Be that as it may, the molecule he obtained can be regarded as an opened-out papaverine molecule. The molecule obtained also has a powerful \(\alpha\)-lytic action.

In the synthesis of isoxsuprine, instead of Külz' phenylalkyl a phenoxalkyl group was attached to the nitrogen, a similar structural change having produced an increase in the \(\alpha\)-lytic activity of related substances.

An isopropyl was chosen to give additional protection to the nitrogen atom by means of a second methyl group.

So far no mention has been made of the fact that isoxsuprine is a racemic mixture (racemate), i.e. a mixture of two kinds of molecules whose structures are mirror images of each other (see below). Nor has it been mentioned that three other racemic mixtures exist whose components have the same structural formula as those of isoxsuprine. This last fact especially has an important bearing on the preparation of an agent having the desired therapeutic properties. As in the preparation of many related substances, these substances tend to occur together. In this case, since they exhibit big differences in their value as drugs, it was important to separate them. Isoxsuprine proved to be the most powerful vasodilator and to have the least effect on the heart. The difficulties involved in the preparation form the subject of the next section.

We end this section with a summary of the characteristics of isoxsuprine as follows:

a) It has a \(\beta\)-sympathomimetic action due to the group

\[
\begin{align*}
\text{OH} & \quad \text{H} \\
\text{C} & \quad \text{N} \\
\text{H} & \quad \text{H} \\
\text{CH}_3 & \quad \text{CH}_3
\end{align*}
\]

Phenylisopropylnoroxephradine

b) It has acquired an \(\alpha\)-sympatholytic action in virtue of the substituted phenoxyalkyl group.

c) It has a spasmylocytic action attributable to built-in analogies with the structure of papaverine.

d) It is effective when given orally owing to the elimination of a hydroxyl group and the protection of the nitrogen by the two methyl groups.

e) Its effect on the heart is slight.

The following section is mainly concerned with the chemical aspect of the investigations; in the final section of the article, we shall return to the pharmacological aspects.

**Preparation of isoxsuprine by asymmetric synthesis**

Sometimes the chemist is faced with the problem of synthesizing a substance without at the same time producing other substances with the same chemical composition (isomers). The same problem arises in an acute form in cases where the substances in question have the same structure as well as the same composition, and differ only in the spatial arrangement or configuration of the component atoms within the molecule (stereoisomers).

To take a simple example, let us consider the reduction of butanon-2 to butanol-2. Figs 3a, b and c represent molecules of these substances. The atom shown occupying a central position in the structure of butanol-2 is known as an asymmetric carbon atom; it is possible for the surrounding atoms
obtained, and these could be separated by fractional crystallization. However, the isoxsuprine yield would be much smaller.

Mechanism of the stereospecific reduction in isoxsuprine production

The asymmetric or stereospecific reduction in the production of isoxsuprine is of theoretical as well as of practical interest; but first it will be as well to give names to the four possible racemates. All have the same chemical structure. We shall take the symbol I, the initial letter of isoxsuprine, to denote this structure, adding some qualification to show which of the various configurations around carbon atoms α, β and γ is being referred to. The accepted prefixes erythro- and threo-, indicating configurations similar to those of erythrose and threose, two well-known sugars, would be suitable for the structures arising around α and β, the two carbon atoms that are close together. The atoms of isoxsuprine, it has been found, are arranged around α and β in the same way as the component atoms of erythrose, and we can therefore give isoxsuprine the name erythro-I. There is a second racemate with the same configuration around α and β as erythro-I; the only difference lies in its opposite configuration around carbon atom γ. We shall refer to this second racemate as alloerythro-I. Accordingly, we can apply the names threo-I and allothreo-I to the two other racemates, which have “threo” configurations around carbon atoms α and β. A diagrammatic explanation is given in fig. 4.

Some processes of synthesis whereby these configurations can be obtained are shown schematically in fig. 5. It can be seen that, with the exception of IV, each of these processes yields either “erythro” or “threo” configurations. This is only to be expected if carbon atom β does, in fact, have a certain effect on the steric course of the reduction process, in the manner described above. As the carbon atom β is unable to influence the configuration of the more distant carbon atom γ, the “allo” forms are always present as a sort of by-product.

It will be clear from the diagram that the course of the synthesis depends on (1) the number of groups attached to the nitrogen atom in the molecule to be reduced, and (2) on the way reduction takes place, i.e. on whether it is reduced by LiAlH₄ or, alternatively, by hydrogen, palladium and carbon. In the order in which the reactions are shown in fig. 5, their products show a complete reversal (from “erythro” to “threo” configurations). For the formation of “threo” configurations it appears to be necessary for the nitrogen atom to have two large groups attached to it; moreover, the reducing agent must be LiAlH₄.

With a view to explaining this reversal let us try first of all to visualize how carbon atom β exercises its influence under conditions of reduction with LiAlH₄.

![Fig. 4. The isomers that are of interest in the synthesis of isoxsuprine (here called erythro-I). Special symbols have been used to represent configurations which are mirror images. The configurations in question arise around the three asymmetric carbon atoms denoted by α, β and γ. 2³ = 8 combinations are possible; these eight stereoisomers constitute four pairs of enantiomers, each pair occurring in a racemate. The names “erythro-I” and “threo-I” have been given to the pairs arising out of combinations between α and β which show structural analogies with erythrose and threose. The prefix “allo” serves to distinguish the two pairs arising out of further combinations with γ.](image)

The reduction reaction of a carbonyl (CO) group with LiAlH₄ is fairly well known. A hydride (H⁻) ion combines with the carbon atom, and an aluminium complex attaches itself to the oxygen. The reaction may take place in the following stages:

\[
\text{LiAlH}_4 \rightarrow \text{Li}^+ + \text{AlH}_4^- \rightarrow \text{Li}^+ + \text{AlH}_2 + \text{H}^-
\]

\[
\begin{align*}
\text{C} &= \text{O} + \text{AlH}_3 \\
\text{C} &= \text{O} - \text{AlH}_3
\end{align*}
\]

\[
\begin{align*}
\text{C} &= \text{O} - \text{AlH}_3 + \text{H}^- \\
\text{H} &= \text{O} - \text{AlH}_3 \\
\text{H} &= \text{O} - \text{AlH}_2 + \text{H}^- \\
\text{H} &= \text{O} - \text{AlH}_2 + \text{H}_2
\end{align*}
\]

\[
\text{H} = \text{O} - \text{AlH}_2 + \text{H}_2 \text{O} \rightarrow \text{H} \rightarrow \text{H} \rightarrow \text{OH} + \text{AlH}_2 \text{OH}
\]

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For a more detailed treatment of asymmetric synthesis, see A possible first step would be to reduce the carbonyl group. Carbon atom α will become asymmetric owing to the reduction process, as does the central carbon atom in butanon-2. Carbon atom β is already asymmetric and it appears to decide the outcome of the reduction process, determining which of the two possible configurations will arise around the new asymmetric carbon atom α.

A small complication is added by the fact that the starting substance is itself a racemate, whose two components differ in their spatial arrangement around carbon atom β. The two configurations influence the reduction process in opposite ways, and consequently this process yields two structures which are mirror images — another racemate, in fact, consisting of two optical antipodes. Thus, in this more complicated case, the asymmetric synthesis decides the outcome of one special racemate instead of the two possible ones.

The next stage in the synthesis of isoxsuprine is to attach the group

\[
\text{H} - \text{C} - \text{C} - \text{O} - \text{CH}_3
\]

to the nitrogen atom; this involves the addition of another asymmetric atom to the two already present. The third asymmetric atom is too far away from the others to allow the principle of asymmetric synthesis to be applied, therefore at this stage of the synthesis ordinary methods are employed. The result is a mixture of two different racemates, which are now separated by fractional crystallization. Separation by this method is possible owing to differences in solubility between the two racemic mixtures — differences which do not exist between the optical antipodes of which each racemic mixture is composed. The question of solubility is linked to that of structure: the separable molecules are not mirror images of one another, whereas the components of each mixture are. (The former are accordingly classified as diastereoisomers, the latter as enantiomers.)

To sum up, the molecule to be synthesized contains three asymmetric atoms α, β and γ; the possible number of stereoisomers is therefore eight. Since these are paired, each pair consisting of mirror-image isomers or enantiomers, four different racemates can be assumed to exist. Isoxsuprine, which is one of the racemates, has been prepared on the one hand by an asymmetric reduction process which excludes two of the possible racemic mixtures, and on the other hand by fractional crystallization, by means of which the two remaining ones were separated.

As can now be inferred, it is possible to synthesise isoxsuprine without using asymmetric reactions. A mixture of all four racemic mixtures would be
Opinions are still divided as to the nature of the aluminium complex, but there is no doubt that it is a bulky one. By making a model of the molecule that undergoes reduction in reaction VI some idea of the effect of attachment of a complex of this kind can be obtained. To an extent dependent on their distance apart, the aluminium complex and the groups attached to the nitrogen atoms will obstruct each other; this effect is known as steric hindrance. The most favourable spatial arrangement is that arising when the aluminium complex is situated between the smallest groups (CH₃ and H — see fig. 6a) attached to the adjacent asymmetric atom, therefore being as far away from the nitrogen atom as possible. The course of the reduction process can be predicted for such a fixed molecule. A hydride ion approaching from under the plane of the drawing meets a methyl group belonging to the neighbouring atom; a hydrogen atom is the only obstacle in the path of a hydride ion approaching from above. The “energy hill” that the ion has to pass over is much lower in the latter than in the former case. The configuration arising in this latter case is in fact the “threo” configuration obtained in practice.

Let us now consider what happens when there is one group less attached to the nitrogen atom. As before, the most favourable position for the aluminium complex is between the smallest groups of the neighbouring asymmetric atom. However, the molecular model now shows that the “effective bulk” of the nitrogen atom and the single group attached to it is roughly the same as that of the methyl group. There is therefore no way of predicting the preferred molecular structure from the size of the groups. Yet there is a second factor which may be decisive: the place of the missing group has been taken by a hydrogen atom which has the tendency to form a hydrogen bridge with an electron donor, available in this case in the form of the oxygen belonging to the carbonyl group. If this hydrogen bond is formed, the position will be as shown in fig. 6b. It will be seen that from the viewpoint of the approaching hydride ion, precisely the opposite situation now prevails. On approaching the carbon atom from below, the hydride ion finds a hydrogen atom in its path; coming from above, it is obstructed by a methyl group. This time the approach from below will be the least difficult, and we may therefore expect the resulting molecule to have the “erythro” configuration.

It may be added that reduction with palladium and carbon rather than with LiAlH₄ is also to be regarded as a factor favouring the “erythro” configuration. Reduction takes place here in an acid environment, in which the nitrogen atom is able to collect an extra proton. Having acquired a positive charge, the nitrogen atom is certain to take up a position close to the negatively polarized oxygen atom in the carbonyl group.

This gives a satisfactory explanation of the stereospecific nature of the reduction reaction and the reversal referred to above. The only thing that still has to be explained is why reaction IV, which yields both configurations, departs from the above described pattern. This can easily be explained. Apart from accelerating the reduction of the carbonyl group, the palladium-carbon catalyst helps to detach the benzyl group. For the molecules where the benzyl is detached before the carbonyl is reduced, the course of the reaction will then be the same as in II and the end-product will have the “erythro” configuration. For the molecules in which the sequence of these events is reversed, “threo” configurations may form.

Now that the synthesis of isoxsuprine has been described and an explanation has been offered for the stereospecific character of the reduction reaction, some experimental evidence for the pharmacological action of isoxsuprine will be given. From now on the drug will be referred to under its trade-name of “Duvadilan” 7). The evidence in question includes findings both from animal experiments and from clinical trials.

7) For pharmaceutical purposes “Duvadilan” is prepared as the hydrochloride of isoxsuprine.
The pharmacology of “Duvadilan”

Animal experiments

Many methods of investigation have been used to determine the effect of “Duvadilan” on blood-vessels. Firstly, its effect on blood flow through an ear of a rabbit has been investigated: the vessels were constricted by administering adrenaline; then “Duvadilan” was given and was found to reverse the constriction effect, the blood flow being restored 8). Secondly, the blood flow was measured in the artery in a rear leg of a dog; fig. 7 shows the percentage increases obtained in the rate of flow as a function of dose 9). Thirdly, the effect of “Duvadilan” was compared with that of a physiological salt solution in experiments on the artery in a leg of a rabbit; the observed changes in blood flow have been plotted in fig. 8 10).

Fig. 7. Arterial blood flow in a rear leg of a dog, as a function of the dose of “Duvadilan” injected into the artery. Blood flow values are expressed as a percentage of the normal value. (After Clark 9.)

Fig. 8. Record of arterial blood flow in a leg of a rabbit. The effect of “Duvadilan”, which was injected in the artery at instant S, was compared with that of a physiological salt solution, administered at instants F. (After Hyman and Winsor 11.)

In addition, experiments have been performed with “Duvadilan” on less accessible regions such as the heart and the brain. The effect on the heart muscle was investigated as follows. Characteristic changes appear in the electrocardiogram of a dog after treatment with a hormone known as “Pitressin” (Parke Davis trade-mark). The changes are caused by a shortage of oxygen: the coronary arteries, which supply the heart, go into a spasm as a result of the administration of “Pitressin”. Fig. 9a is an electrocardiogram showing this effect. Fig. 9b

Fig. 9. Two electrocardiograms, recorded at an interval of eight days, showing the response of a dog to treatment with a) “Pitressin”, which induced coronary spasm, and b) “Pitressin” and “Duvadilan”. The traces to the left of the first vertical division were obtained before administering “Pitressin”; the traces between the vertical divisions were recorded immediately after, and those on the right five minutes after “Pitressin” was administered. On occasion b) the dog received a subcutaneous injection of 0.25 mg of “Duvadilan” per kg of body weight 15 minutes before the “Pitressin” was administered. It is clear that “Duvadilan” suppresses the effect of “Pitressin”. (After Brücke 8.)
<table>
<thead>
<tr>
<th></th>
<th>Reaction 1</th>
<th>Reaction 2</th>
<th>Product 1</th>
<th>Product 2</th>
<th>Product 3</th>
<th>Product 4</th>
</tr>
</thead>
</table>
| I | \[
\text{HO-CH}_2\text{-C-C=NH}_2
\] | reduction of C=O | \[
\text{HO-CH}_2\text{-C-C=NH}_2
\] | addition | \[
\text{HO-CH}_2\text{-C-C=NH}_2
\] | {erythro-I} + {alloerythro-I} |
| II | \[
\text{HO-CH}_2\text{-C-C=NH}_2
\] | reduction of C=O | \[
\text{HO-CH}_2\text{-C-C=NH}_2
\] | \[
\text{HO-CH}_2\text{-C-C=NH}_2
\] | {erythro-I} + {alloerythro-I} |
| III | \[
\text{HO-CH}_2\text{-C-C=NH}_2
\] | reduction of C=O | \[
\text{HO-CH}_2\text{-C-C=NH}_2
\] | \[
\text{HO-CH}_2\text{-C-C=NH}_2
\] | {erythro-I} + {alloerythro-I} |
| IV | \[
\text{HO-CH}_2\text{-C-C=NH}_2
\] | reduction of C=O | \[
\text{HO-CH}_2\text{-C-C=NH}_2
\] | splitting off | {erythro-I} + {alloerythro-I} + {threo-I} + {allothreo-I} |
| V | \[
\text{HO-CH}_2\text{-C-C=NH}_2
\] | reduction of C=O | \[
\text{HO-CH}_2\text{-C-C=NH}_2
\] | splitting off | {erythro-I} + {alloerythro-I} + {threo-I} + {allothreo-I} |
| VI | \[
\text{HO-CH}_2\text{-C-C=NH}_2
\] | reduction of C=O | \[
\text{HO-CH}_2\text{-C-C=NH}_2
\] | splitting off | {erythro-I} + {alloerythro-I} + {threo-I} + {allothreo-I} |

Fig. 5. Reactions yielding isoxsuprine (erythro-I) and the isomeric racemates alloerythro-I, threo-I and allothreo-I. All the starting substances can be produced by conventional methods.
was recorded a few days later; on this occasion the same dog was given a subcutaneous injection of “Duvalidan” before being treated with “Pitressin”. In this case the latter drug appears to have had no effect 8).

To illustrate the effect on the blood supply to the brain, experiments have been performed in which the cerebral blood-vessels of dogs and cats were photographed via a window in the top of the skull 11). Afterwards the diameters of the vessels appearing in the photographs (fig. 10) were measured. Table II gives the results of an experiment of this kind in which the animal was injected with 0.1 mg of “Duvalidan” per kg of body weight. It is evident from this that “Duvalidan” dilates the blood-vessels of the brain.

The effect of “Duvalidan” upon the heart was measured from the heart rate (number of beats per minute) as determined from an electrocardiogram. Following intravenous administration of 0.2 mg of “Duvalidan” per kg of body weight, the heart rate of non-anaesthetized dogs was found to increase rapidly at the outset, reaching twice the starting value and thereafter slowing down again; 70 minutes after medication it had fallen to 24% above the starting value 8).

It should be borne in mind that the speed of the heart can alter for two reasons: it may change owing to direct action on the heart, and also in response to a change in blood pressure. This latter possibility must be excluded if it is desired to record changes in heart rate that are a true measure of direct action on the heart. A heart-lung preparation is used for this purpose, reflex acceleration being eliminated by cutting the nerve connections that make it possible. In a preparation of this kind, the heart rate was found to increase by between 20% and 50% following administration of 5 mg of “Duvalidan”. The corresponding increase in the rate at which blood was pumped around the body (the “heart minute volume”) was about 20% 8).

On the basis of these findings “Duvalidan” may be said to have a comparatively weak direct action on the heart.

Clinical evidence

Numerous medical practitioners have reported the results of “Duvalidan” treatment of their patients. A check on whether blood flow has really improved or not is provided by a technique known as plethysmography which allows the blood stream in a given part of the body to be measured from the outside.

There is a pressure difference of about 100 mm Hg between the blood entering and the blood leaving a part of the body such as a finger, foot, arm or leg. This difference is that between the arterial and venous pressures. By applying an inflatable cuff to these parts of the body it is possible to stop the flow of blood through the vein while not interfering, or
hardly interfering, with that through the artery. The cuff is inflated to a pressure higher than the venous but lower than the arterial pressure. The result is that the volume of the affected part increases. The change in volume per unit time immediately after blockage is equal to the rate of arterial blood flow.

One way of measuring the change in volume is by means of an inelastic container into which the limb or part is inserted and then sealed off from the exterior, the space thus enclosed being connected to a volumometer. Blood flow in the limb or part can be determined from a curve showing changes in the enclosed volume, as traced by the volumometer.

The tracings shown in fig. 11 were obtained in this way. They record blood flow in the calf of a patient before and after "Duvadilan" was injected into the artery supplying the calf. It will be seen that the slope of the curve increased by 80% after the injection. As a control, increases in the volume of the left calf were recorded at the same time (plethysmograms c and d). The slope of the trace is a measure of the blood flow. In the right calf this increased by 80%, in consequence of the "Duvadilan" injection. The effect of the drug when administered in this way does not extend to the other limb.

The heartbeat shows up in the fluctuations of the plethysmographic trace, which can accordingly serve also as a record of heart rate. (After Hyman and Winsor 10.)

Other data relating to the effects of "Duvadilan" have been obtained by using the drug to treat vascular disorders involving "intermittent claudication" (i.e. occasional limping). Sufferers from such disorders are prevented from walking long distances by the onset of spasm in the blood-vessels. The average distance the patient is able to walk without experiencing pain is an inverse measure of the seriousness of the condition. "Duvadilan" treatment has been found to increase the average walking distance.

"Duvadilan" has also been used to treat necrotic skin diseases in which, owing to an inadequate blood supply, patches of skin die. Administration of "Duvadilan" has been found to promote the healing of these necrotic skin areas.

An impression of a drug's action on the heart can be obtained not only by taking the pulse or inspecting an electrocardiogram but also by measuring variations in blood pressure. It should be explained that the pressure of blood in the circulatory system alternates in the rhythm of the heartbeat between two values, the systolic and the diastolic pressure. The amplitude of the pressure change (i.e. the systolic minus diastolic pressure, otherwise known as "pulse pressure") is related to the amount of blood forced into circulation with each contraction of the heart. This amount is called the stroke volume. Fig. 12 shows blood pressure values before and after a
“Duvadilan” injection. It reveals a slight increase in pulse pressure after the injection, which can be taken as an indication that the stroke volume had increased to some extent. Further evidence in this direction is provided by radiographs showing the outline of the heart wall. The displacement of the heart wall as recorded by this technique, known as X-ray kymography, can be taken as a basis for calculating the stroke volume. On this basis the stroke volume has been found to increase by about 7% after a slow intravenous injection of 10 mg of the vasodilator.

The effect of “Duvadilan” on the heart minute volume has also been investigated. As already indicated, the minute volume is the output of blood from the heart over a period of one minute; it is therefore the product of stroke volume and heart rate. The minute volume can be measured by injecting a small quantity of radioactive serum into the bloodstream at some point, and then recording, by means of a detector placed above the heart, for example, the rate at which radioactive material is passing this second point. From results of such measurements it has been calculated that the minute volume increases by about 30% after a slow intravenous injection of 10 mg of “Duvadilan”. Evaluation of electrocardiographic and other direct evidence of heart rate changes shows an increase of about 20% in the number of beats per minute following an intramuscular injection of 10 mg of “Duvadilan”. This figure agrees more or less with those for stroke and minute volume. All in all, these data reveal that “Duvadilan” has a relatively small effect on the heart, in human beings as well as in laboratory animals.

In conclusion it may be mentioned that the drug is being employed on an increasing scale in obstetrics. “Duvadilan” appears to be very effective for relieving uterine spasm, in virtue of its β-mimetic action and probably of its papaverine-like spasmylytic action as well. Indeed, many of the reports on “Duvadilan” have come from obstetric departments, particularly during the last few years. Thus, having first gained recognition as a vasodilator, “Duvadilan” is proving to be of value as a spasmylytic agent.

As to further developments in this field, it will be recalled that “Duvadilan” is composed of two optical antipodes; investigations now in progress are concerned with the individual contributions of the component enantiomers to the effects of “Duvadilan”. These may be expected to provide new knowledge that will certainly be of scientific interest, and may possibly be of medical value.

Summary. “Duvadilan” (isoxsuprine), which was introduced a few years ago, is a drug with a specific vasodilating action and is of value for treating certain vascular and other disorders. It is suitable for oral administration as well as by other routes. Its pharmacological action can be regarded as comprising a β-sympathomimetic, an α-sympatholytic and a spasmylytic component. These three properties of isoxsuprine can be explained with reference to the properties of substances to some extent analogous with it, namely adrenaline, noradrenaline, ephedrine, papaverine, etc. Isoxsuprine is a racemic mixture (racemate) which, during synthesis, has to be separated from three other racemates, all the substances concerned being isomers of each other. One stage of separation is effected by exploiting stereo-specific reduction (using LiAlH₄, or alternatively H₂, Pd and C). A mechanism is suggested to explain the relevant reaction. The concluding section contains data on the pharmacology of “Duvadilan”, derived from animal experiments and clinical practice.
The photograph shows 5-kW communication transmitters being assembled in the Huizen (Netherlands) factory of N.V. Philips’ Telecommunicatie-Industrie. Transmitters of this type consist of a power-supply cabinet, one or more radio-frequency cabinets, and possibly a modulator cabinet. Each RF cabinet is tuned to a fixed frequency. When propagation conditions make it necessary to change the frequency, two manual operations are all that is needed to switch from the cabinet in use to another.

The mechanic is seen here behind the second of three frames slid out of their cabinets. He is fitting the HT cable that connects the decoupling capacitor to the output stage. The latter, which is not yet in place, is mounted on a separate chassis to make it interchangeable.

Above the drive unit in the front cabinet can be seen the airducts for the cooling of the two output valves, which are in push-pull.