BRITISH MEDICAL JOURNAL

LONDON SATURDAY APRIL 2 1938

THE ALKALOID EPHEDRINE*

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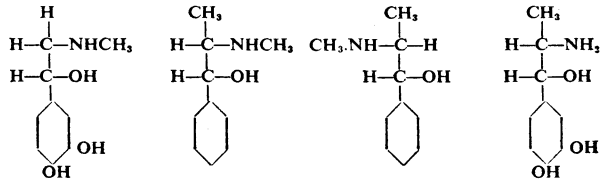
The alkaloid ephedrine is present in extracts of various plants belonging to the genus *Ephedra,* which all grow in roughly the same latitude in Northern China, Northern India, and Spain. One species has been used as a drug in China for about 5,000 years under the name of "ma huang." The plant consists almost entirely of bundles of green stems lying parallel without much branching. The leaves are reduced to small dry scales arranged in twos or threes round the stem at intervals, so that the plant looks rather like an equisetum. In actual fact the ephedras are gymnosperms, and are therefore related to the pines and firs, whereas the equisetums are not flowering plants at all, and are very distant relations of the ephedras.

The chemical structures of ephedrine and pseudo-ephedrine are here shown. These alkaloids, both of which



are present in the green stems of some kinds of ephedra, are optical isomers of one another and closely related to adrenaline. The molecules of ephedrine and pseudo-ephedrine each contain two asymmetric carbon atoms. There are therefore four optical isomers. The two laevorotatory isomers are included in the formulae given here. The dextro-isomers are the mirror images of these. The difference between ephedrine and pseudo-ephedrine depends on the position of the two asymmetric carbons relative to one another, and is represented graphically by drawing $-NHCH_3$ and $-OH$ near to one another in the case of ephedrine and opposite to one another in the case of pseudo-ephedrine: *l*-ephedrine and *d*-pseudo-ephedrine are the natural isomers, and are more active pharmacologically than the other isomers.

Early References to Ma Huang

The history of scientific work with ephedrine is shown graphically in the chart, which is based on a bibliography by B. E. Read showing all the papers on the subject up to 1934. The rate at which papers on ephedrine appeared is plotted against time. The first pharmacological experiments were carried out in China in 2760 B.C. by the Emperor Shen Lung, who tasted all the drugs in the pharmacopoeia and classified them accordingly. Ma huang was classified as a "medium" drug. The next surviving reference was published about 2,500 years later. This represents a big gap in the literature, but it is probable that many references from this period have been lost. After the beginning of the Christian era the rate of publication increased from about one paper per century to four papers a century in the period 1500 to 1880.

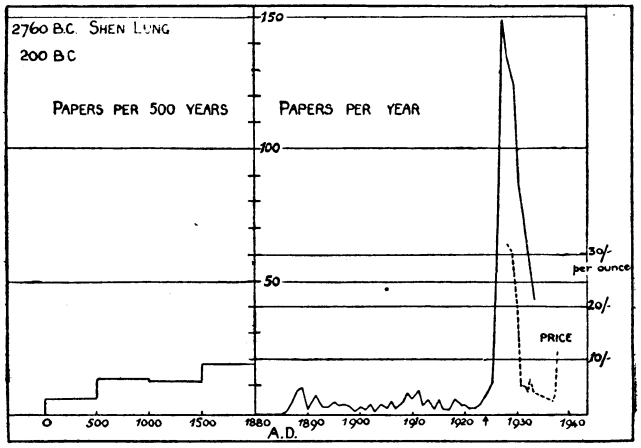


Chart showing the history of scientific work with ephedrine.

A famous pharmacopoeia written in China in A.D. 1596 says that ma huang is of use as a circulatory stimulant, diaphoretic, antipyretic, and sedative in cough. Modern observations confirm most of this. Ephedrine does stimulate the circulation under certain conditions, and has been found beneficial in whooping-cough. Its diaphoretic effect has been observed in man, but attempts to demonstrate it in animals have been unsuccessful.

Modern Literature

After 1880 the rate of publication increased so rapidly that it is necessary to plot the results on a different scale.

Ephedrine was isolated by the Japanese worker Nagai (1887) and given the name by which it is known to-day. Pharmacological investigations showed that large doses had toxic effects, and ephedrine acquired a reputation as a dangerous poison. Its mydriatic action was discovered and studied in detail. Takahashi and Miura (1892) came to the conclusion that ephedrine dilated the pupil by stimulating the sympathetic nerves. It is remarkable that they should have reached this conclusion so long ago, before anything was known about adrenaline, or even about the properties of suprarenal extracts. The only other substance they knew of as a drug acting similarly was cocaine. At about this time ephedrine was put on the market in Europe as a mydriatic. It was apparently not employed for other purposes, and its use soon died out. For many years little research was done except by chemists, who worked out the details of the chemical structure and had synthesised all the optical isomers by 1920.

*Sidney Ringer Memorial Lecture delivered at University College Hospital Medical School, March 8, 1938.

The pharmacology of ephedrine was reinvestigated in Japan by Amatsu and Kubota in 1917. It was shown to have sympathomimetic effects like those of its chemical relative adrenaline. Ephedrine was put on the market in Mukden as a remedy for asthma, but since the results were published in Japanese they attracted no attention in the Western world, and were even unknown to Chen and Schmidt when they started to work on ma huang in 1923. A Chinese druggist told them that this was a really active drug, and would be likely to prove interesting. They therefore made extracts of the plant, injected them into dogs, and observed the resulting rise of blood pressure. They isolated the alkaloid and showed that it had adrenaline-like properties before they discovered that ephedrine had been isolated and studied before. Nevertheless this work of Chen and Schmidt had a very important effect, because it aroused interest in ephedrine and stimulated the production of papers. Their original paper was published in America in 1924. By 1927 the rate of publication had risen from less than ten papers per year to about 150. Thereafter the rate slowly fell, but more papers are still produced each year than before Chen and Schmidt's article appeared.

Ephedrine provides an example of the practical application of pharmacological discoveries in clinical medicine. It is interesting to note that fundamental observations on its action were made on three separate occasions before they caught the imagination of the world. Once the imagination was caught the demand for ephedrine was great, and the world now consumes about ten tons a year —corresponding to about 1,000 tons of ma huang.

Synthetic ephedrine was introduced in 1927—the year when interest in ephedrine was at its height—under the name of ephetonin. This preparation consists of a racemic mixture of the two optical isomers, and is therefore slightly less active than the natural laevo-ephedrine. Competition brought the price down from 33s. 4d. an ounce in June, 1929, to 5s. 10d. an ounce a year later and 2s. 6d. in 1936. Thousands of tons of ephedra were exported from China, India, and Spain, mainly to America, where very large stocks are held now; and someone must be making a lot of money, because the wars in Spain and China have sent the price up to about 12s. an ounce. Synthetic ephedrine has thus come into its own, and it has become economically possible to sell synthetic laevo-ephedrine, which is presumably equivalent in all respects to the natural product. This fact has probably kept the price of natural ephedrine from rising still higher.

The Pharmacological Effects of Ephedrine

The pharmacological effects of ephedrine resemble those of adrenaline in many ways. For example, under suitable conditions ephedrine raises the blood pressure by constricting the blood vessels and stimulating the heart. It dilates the pupil, dilates the bronchi, inhibits the intestine, and raises the blood sugar. In large doses it has various other effects, which have been attributed to an indiscriminate stimulation of smooth muscle and to stimulation of autonomic nerve ganglia. I am not concerned with these effects now, nor with its action on the central nervous system, but with the adrenaline-like action of small doses. The actions of the two drugs resemble one another in many ways, but various differences have been noticed. I propose to give a list of these now and to discuss them more fully later.

1. Ephedrine is more stable and has a more prolonged action than adrenaline, and, unlike adrenaline, it is effective when given by the mouth.

2. Section of the sympathetic adrenergic nerves to certain tissues, followed by degeneration, increases the effect of adrenaline and diminishes that of ephedrine. An injection of cocaine has similar effects.

3. Ephedrine has often been found to have much less action on isolated tissues than might have been expected from its effects in the body.

4. If the same dose of ephedrine is given repeatedly the effect diminishes with each successive dose. This is not true of adrenaline. This immunity lasts for only a few hours. Rabbits which have received injections of ephedrine every day for several months still react to ephedrine with a rise of blood pressure (Rühl, 1929).

It is evident that although the actions of ephedrine resemble those of adrenaline superficially, the two actions are not exactly the same, and various workers have come to the conclusion that the two drugs act on different parts of the sympathetic mechanism. I want to tell you of some new observations, and of a new theory which explains some of the peculiarities of the action of ephedrine.

The Cholinergic and Adrenergic Nerve Groups

Before discussing these new facts I propose to recall to your minds certain recent advances in our knowledge of the mode of action of motor nerve endings. Evidence has been advanced that most, if not all, motor nerves produce their effects by liberating a chemical substance at their ends. This chemical substance carries the impulse across the synapse and, by its pharmacological action, produces the effects which were formerly supposed to be produced by the nerve itself. Motor nerves can be divided into at least two classes according to the nature of the chemical substance liberated. Most motor nerves liberate acetylcholine, but some of them liberate adrenaline or a closely allied substance. Sir Henry Dale has suggested that the former group should be called cholinergic and the latter group adrenergic. These words supplied a real need and have spread all over the world.

Some years ago, when I was working in Sir Henry's laboratory, I helped to identify the substance liberated at cholinergic nerve endings as acetylcholine. Chang and I (1933) showed that, by suitable pharmacological tests, it was possible to distinguish acetylcholine from other choline esters, and then Feldberg and I applied these tests (1934) to the substance liberated in a sympathetic ganglion and identified it as acetylcholine, as distinct from other choline esters. Later similar results were obtained in experiments with other nerves, and more recently I have been trying to apply tests to discover whether or not the substance liberated by adrenergic nerves is adrenaline. This question is particularly interesting to us because the theory that nerves liberate adrenaline was first advanced by Professor T. R. Elliott in 1904. It is also particularly important because Cannon and Rosenblueth (1937) have presented evidence that two different substances are liberated on stimulating different kinds of adrenergic nerves. They believe that both substances are similar to adrenaline, but that neither of them is identical with it.

Substrate Competition

The experiments with acetylcholine were made much easier owing to the discovery that eserine (physostigmine) preserved acetylcholine from destruction in the body. In the absence of eserine the acetylcholine liberated at nerve endings was apt to be destroyed before it could be detected, but when eserine was added the acetylcholine was preserved and the experiments were successful. The enzyme which destroys acetylcholine is known as choline esterase, and it is probable that the eserine acts by combining with choline esterase and blocking it up (Easson and Stedman, 1936). The eserine molecule is in certain respects similar to the acetylcholine molecule, and choline esterase does not seem to know the difference. The molecules of enzyme combine with eserine, which is comparatively stable, and are therefore no longer free to devote them-

selves to the destruction of acetylcholine. This chemical phenomenon is known as substrate competition. A substance which would preserve adrenaline in the body in the same sort of way that eserine preserves acetylcholine might therefore be expected to facilitate experiments with adrenergic nerves as eserine has facilitated experiments with cholinergic nerves. Such a substance would probably be similar in chemical structure to adrenaline, but more stable. There is reason to believe that ephedrine acts in this way.

The adrenaline molecule may meet its end in various ways. The catechol group makes it unstable. In watery solution its tail curls up and becomes attached to its head, forming a red indole derivative. This change is inhibited by blood and is not the only fate of adrenaline in the body, which contains several enzymes capable of destroying adrenaline in different ways. Various workers have recently been drawing attention to one particular enzyme, known as amine oxidase, which destroys adrenaline, and various other amines, by removing the nitrogen. Blaschko, Richter, and Schlossmann (1937) have shown that ephedrine is not destroyed by amine oxidase, but that in the presence of ephedrine the enzyme is prevented from destroying adrenaline. They attribute this action, like that of eserine, to substrate competition.

These experiments of Blaschko, Richter, and Schlossmann were carried out with minced tissues, and the rate of destruction of adrenaline was calculated from measurements of the increased oxygen uptake due to adrenaline. The results clearly show the presence in certain tissues of an enzyme which destroys adrenaline, and which is inhibited by ephedrine. They throw no light on the part played by the enzyme in the body, but they show that if this enzyme should turn out to be the agent which destroys adrenaline when it has produced its effect, ephedrine would be likely to inhibit this destruction and play a part similar to that played by eserine at cholinergic nerve endings. My main purpose is to discuss the evidence for the theory that amine oxidase and ephedrine do in fact act in this way. This theory explains some of the peculiarities of the action of ephedrine, and I therefore propose to return to these peculiarities and discuss their relation to the theory.

Peculiarities of the Action of Ephedrine

In the first place, the fact that the actions of ephedrine are more prolonged than those of adrenaline might be explained on the theory that the action of adrenaline is normally controlled by the action of amine oxidase, and that ephedrine owes its prolonged action to its immunity to this enzyme. The prolonged action of ephedrine could, however, be explained in other ways, since ephedrine is normally resistant to other destructive agents besides amine oxidase.

In the second place, experiments on the effect of the degeneration of nerves confirm the theory that some of the actions of ephedrine resemble those of eserine. After degeneration of its nerve supply the pupil becomes more sensitive to acetylcholine and adrenaline, but much less sensitive to eserine and ephedrine. After degeneration of the nerves the liberation of chemical transmitters presumably ceases, so that substances whose actions depend on preservation of the transmitter naturally lose their effect. The action of small doses of ephedrine on the cat's nictitating membrane, on the other hand, is increased by degeneration of the nerves (Bülbring and Burn, 1937). In this case ephedrine presumably acts exactly like adrenaline.

The third peculiarity of ephedrine which I mentioned is the fact that it often has less action on isolated tissues than might be expected from its activity in the body.

Schaumann (1928) suggested that this difference might be due to the presence of adrenaline in the body and its absence in isolated tissues. He found that when adrenaline, in a concentration of one in ten millions, was added to the Ringer's solution perfusing a frog's legs the addition of a similar concentration of ephedrine caused marked vasoconstriction. In the absence of adrenaline these concentrations of ephedrine had no effect. Burn (1932) obtained similar results when dogs' legs were perfused with blood. Incidentally Schaumann observed that when high concentrations of ephedrine were added to perfusion fluid containing adrenaline the ephedrine caused vasodilatation. This observation falls in line with various others which show that *high* concentrations of ephedrine antagonize adrenaline. These observations led Schaumann to the discovery that the injection of ephedrine increased the effect of the subsequent injection of adrenaline on the blood pressure of rabbits and dogs. Similar results have been obtained by others. Csépai and Doleschall (1928) found that ephedrine increased the effect of adrenaline on the blood pressure of man. On the other hand, Curtis (1929) observed that large doses of ephedrine antagonized the effect of adrenaline on the blood pressure of dogs. Reinitz (1929) found that low concentrations of ephedrine increased the effect of adrenaline on the rabbit's uterus. High concentrations had the opposite effect. Pak and Tang (1933) discovered that the application of ephedrine to a rabbit's conjunctiva sensitized the pupil to the subsequent local application, or intravenous injection, of adrenaline. Kwiatkowski and I have recently seen similar effects in a frog's heart, a rabbit's ear, and a cat's nictitating membrane.

Low concentrations of ephedrine have thus been shown to increase the actions of adrenaline in much the same way that eserine increases the actions of acetylcholine. This effect of eserine is generally attributed to the inhibition of choline esterase, but so far as I know no one has suggested that the corresponding effect of ephedrine is due to the inhibition of an enzyme. Now that Blaschko, Richter, and Schlossmann have demonstrated the inhibition of amine oxidase by ephedrine *in vitro* the evidence is as complete in the case of ephedrine as it is in the case of eserine. The possibility of other explanations must, however, be borne in mind.

These results provide a new method of studying the mechanism at an adrenergic nerve ending. Eserine increases the action of cholinergic nerves, presumably by inhibiting the destruction of the acetylcholine which they liberate. Kwiatkowski and I have found that ephedrine has a similar action on the adrenergic nerves in a frog's heart, a rabbit's ear, and a cat's nictitating membrane.

The Effect of Ephedrine on Adrenaline and Adrenergic Nerves

I hope I have convinced you that, under appropriate conditions, ephedrine potentiates the actions of both adrenaline and adrenergic nerves. If this effect is due to the protection of adrenaline from destruction, ephedrine should increase the amount of detectable adrenaline liberated on stimulation of adrenergic nerves. Kwiatkowski and I have obtained direct evidence of this in experiments with the perfused ears of rabbits. For these experiments the ear was perfused with the solution known as "Locke-Ringer" by means of a special device which ensured that the rate of flow was practically constant and was not affected by stimulation of the nerves. A sensitive colorimetric test for adrenaline devised in my laboratory by F. H. Shaw (1938) was applied to the outflowing fluid. This test is not affected by ephedrine, and makes it possible to distinguish adrenaline from closely allied sub-

stances. When the nerves were stimulated in the presence of ephedrine an adrenaline-like substance was detected in much higher concentration than had been possible without ephedrine.

These results show that ephedrine protects the substance liberated by the nerves, and support the theory that the sensitization of adrenergic nerves is due to this effect. Since amine oxidase is the only enzyme which has so far been shown to be inhibited by ephedrine they suggest that this enzyme is present near the nerve endings and constitutes the normal mechanism for destroying the chemical transmitter. I think, however, that the main importance of the results is that they have made it possible to obtain the chemical transmitter in higher concentrations than before and to discover something of its properties. It has been suggested, for example, that the substance liberated by adrenergic nerves such as those in a rabbit's ear is not adrenaline, but noradrenaline. By means of a specific modification of the colorimetric test this possibility has been excluded.

Ephedrine and Adrenaline Antagonism

I have said nothing so far about the explanation of the fourth peculiarity of ephedrine—the diminishing effect of successive doses—nor about the action of large doses in antagonizing adrenaline. I believe that these effects are two aspects of the same phenomenon. Schaumann observed both effects when he perfused frogs with Ringer's solution containing adrenaline. Successive doses of ephedrine produced less and less vasoconstriction, and eventually large doses caused vasodilatation. In this preparation the vasoconstrictor action of ephedrine was probably due entirely to inhibition of amine oxidase, since there was no effect in the absence of adrenaline. The inhibitory effect can be explained on the theory that ephedrine combines with the same receptors in the muscle as adrenaline, but produces no effect when so combined. The receptors thus become blocked up so that adrenaline cannot affect them. Similar explanations have been put forward to account for the antagonistic actions of a number of different pairs of drugs. I think that such a theory was first suggested in 1880 by Ringer and Morshead to explain the antagonism of atropine and pilocarpine on the frog's heart. It is similar to the theory of substrate competition, which I have already discussed. Curtis (1929) put forward this theory to account for the action of large doses of ephedrine in antagonizing adrenaline. He could not explain the diminishing effect of successive doses of ephedrine in this way, because he supposed that ephedrine was acting in the same manner as adrenaline, and it would not seem likely that ephedrine could antagonize itself by keeping itself out, so to speak. The most reasonable explanation now seems to be that ephedrine antagonizes itself by keeping out the adrenaline through which it would otherwise have acted.

Uses of Ephedrine

Pharmacology can sometimes point the way to therapeutics, but it is often very difficult to predict what the end of the journey will be like. I believe that the first sample of ephedrine to enter University College Hospital did so in 1925—in my pocket. Little was known at that time about ephedrine except that it produced prolonged stimulation of the sympathetic and was active when given by the mouth. Perhaps it should have been possible to foresee most of the clinical applications, but a knowledge of these has come gradually and rather erratically. I remember thinking that ephedrine might be of value in Addison's disease. Experience showed that it is not.

The oldest clinical use of ephedrine depended on its action on the pupil. If a 6 per cent. solution is dropped in the eye the pupil dilates in about an hour, and stays dilated for five to twenty hours. The pupil still reacts to light and accommodation is not affected. Ephedrine has been employed for ophthalmological diagnosis in preference to atropine or homatropine. It is said not to increase the intra-ocular pressure.

The best-known use of ephedrine is probably in the treatment of asthma. It dilates the bronchi and relieves attacks in much the same way as adrenaline, compared with which it is less often effective; but its action lasts longer, and it can be taken by the mouth. I suspect that many people take too much. An eighth of a grain is often enough. It has been found to relieve whooping-cough. It has also been used with a certain amount of success in other allergic conditions such as hay fever and urticaria. It is used to prevent, or cure, serum sickness. It is having rather a vogue now for local application to the nose, where it produces vasoconstriction and dries up secretions. It is of little or no value in vasomotor shock, but it is employed to counteract the fall of blood pressure due to a spinal anaesthetic. Ephedrine has been used successfully in both the prevention and the cure of the attacks of heart-block known as Stokes-Adams's syndrome. This is an effect which might have been predicted, because an improvement in conduction in the bundle of His is one of the effects of sympathetic stimulation.

Ephedrine has been widely and successfully used to prevent the pathological sleep of narcolepsy, though it is being replaced for this purpose by its more efficient chemical relative known by the name of benzedrine. The fact that benzedrine produced this effect was discovered suddenly and accidentally, but the history of this use of ephedrine is long and complicated. In 1913 Airila tested the action of the series of drugs in waking up rabbits which had been anaesthetized with chloral hydrate. He knew that cocaine had a stimulant action on the central nervous system, and found that it would wake up his anaesthetized rabbits. He also knew that cocaine stimulated some parts of the peripheral sympathetic system, and thought that the two effects might be associated. So he tested other sympathomimetic drugs for their power to wake up rabbits. His theory was wrong, because adrenaline had no action, so that the two effects were not necessarily associated, but ephedrine woke the rabbits up. Later work has shown that ephedrine has complex effects on the central nervous system which are not yet understood. It has been found to awaken animals anaesthetized with avertin, paraldehyde, and evipan. It also restores reflexes and stimulates the respiration, but it seems to have the opposite effect on animals anaesthetized with barbitone or phenobarbitone. Clinically ephedrine has been found to encourage sleep in children and to prevent it in adults. It causes euphoria in some people. The discovery of these facts led to the use of ephedrine in narcolepsy.

The use of ephedrine in myasthenia gravis could not, I think, have been predicted. Its value in this disease was discovered accidentally by Harriett Edgeworth (1930), who was both a scientist and a victim of the disease. She was taking ephedrine for dysmenorrhoea and found it had a very good effect on her myasthenia. This observation was confirmed, but not explained. It has tended to be overshadowed by the marked effect on this disease of physostigmine and its relations. The use of ephedrine in dysmenorrhoea was originally based on the questionable

theory that dysmenorrhoea was due to parasympathetic over-activity. Favourable reports have been published.

Ephedrine is also employed in enuresis. Its effectiveness—if it is indeed effective—might be explained in the same way, but it is more likely that the action is on the central nervous system. Perhaps I should add that, like so many drugs, ephedrine has been recommended as a cure for sea-sickness.

The toxic effects ascribed to overdosage are general nervousness and insomnia and tremor, vomiting and sweating, palpitations, urinary retention, and skin eruptions. When large doses are given to rabbits over a long period they cause enlargement of the heart with pronounced degenerative changes (Rühl, 1929).

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The psychological reactions of thirty "problem" children who received benzedrine sulphate for one week are recorded by C. Bradley (*Amer. J. Psychiat.*, November, 1937, p. 577). In fifteen there was spectacular improvement. Many became much less emotional, without, however, losing interest in their surroundings; they also experienced a sense of well-being. In this group were some children who had previously expressed their irritability in group activities by noisy, aggressive, and dominating behaviour; these became more placid and easy-going under the influence of benzedrine. No significant changes were detected in the blood or body weight, but in six cases the onset of sleep was delayed for the first night or so. Loss of appetite and nausea were shown by a few children only. The behaviour changes reached their maximum during the second and third hours after the administration of the drug, and there was a gradual reversion to the state normal for the particular child during the following six to twelve hours. In all cases the full effects became manifest on the first day of administration, continued daily through the week, and disappeared as soon as the drug was discontinued. The optimum dose was found to be 20 mg. In eight cases gastro-intestinal symptoms were provoked; these eight children were given subsequently daily doses of 10 mg. for a week; two derived no benefit, suggesting that the lowest dose which they could tolerate was therapeutically ineffective. No relationship was established between the children's ages or weights and their reactions to benzedrine. The author advises that this drug should be further tested experimentally before being recommended for the treatment of behaviour-problem children; he suggests that its action might be explained on the lines that it rectifies the impaired control activity which has given rise to disorders of behaviour.

AMENORRHOEA: ITS AETIOLOGY AND TREATMENT*

BY

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The data accruing from the present-day intensive study of sex physiology are at times bewildering and often overwhelming in their complexity. Nevertheless, from the conflicting mass of scientific evidence new facts are emerging which are furthering our knowledge of the processes associated with menstrual and reproductive function, and new therapeutic agents are gradually being added to the armamentarium of the clinician. These new therapeutic agents have been enthusiastically accepted and applied in the treatment of all gynaecological conditions that might be associated with underlying endocrinal disturbances. In some such conditions they are eminently successful—for example, in many post-menopausal disorders—but endocrine therapy has not fulfilled the early promise predicted. Disappointing response to treatment, however, may not be due to faulty or ineffective preparations but rather to their indiscriminate application. Without some knowledge of the therapeutic action of the various sex hormones and their relation to the mechanism of menstrual periodicity therapy must in the main be conjectural. In this paper I am dealing with a study of ninety-seven cases of amenorrhoea, most of which have been investigated as fully as present-day methods permit.

Methods of Investigation

1. *History.*—A full anamnesis is of great importance. Special attention should be directed to the state of previous health and to the occurrence of any unusual circumstances present immediately before or at the time of cessation of menstruation. Frequently a history of change of occupation, domestic worry, grief, or social estrangement is obtained which has an important bearing in regard not only to aetiology but also to prognosis and treatment. Details of previous menstrual rhythm and loss should be elicited. The presence or absence of menstrual molimina may also be important as regards prognosis; their presence is rather more favourable than otherwise. Information should be obtained as to any increase or loss of weight and its association with the onset of the amenorrhoea.

2. *Detailed Examination of the Reproductive Tract.*—Whilst the whole reproductive tract must pass under review, the size of the uterus requires special attention, as in many cases this gives an approximate index of ovarian function. It is important, where possible, to examine the endometrium histologically—first, to exclude tuberculosis, and, secondly, to obtain information regarding ovarian activity.

3. *Radiographs of the Sella Turcica.*—Though pathological changes of the sella are rarely found, we may discover in some cases distortion of the sella pointing to gross pituitary disease. Occasionally amenorrhoea is one of the initial features in pituitary lesions, and it is on account of the cessation of menstruation that the patient may seek medical advice.

4. *Estimation of the Basal Metabolic Rate.*—This is the only available method of forming an approximate estimation of thyroid function. As the function of the

* Lecture delivered (by invitation) at the British Postgraduate Medical School, Hammersmith Hospital, London.