As is generally known, ephedrine is an alkaloidal active principle obtained from a Chinese herb which, under the name of Ma Huang, has been used by native physicians for some 5000 years. It was one of the drugs which is said to have been tasted by the Emperor Shen Nung, who placed it in the "medium class". It is mentioned in the Pentasao Kang Mu, the Chinese dispensatory, written in 1596 by Shih-Cheng Li. According to this authority Ma Huang is of value as a circulatory stimulant, diaphoretic, antipyretic, sedative in cough, and it is an ingredient of many famous prescriptions. An English translation of the ancient Chinese records can be found in the paper by Hagerty and Woo.

Plants similar to, if not identical with Ma Huang have been employed as medicines since remote antiquity in other parts of the world. Thus, it is said (Berendes) that Greek physicians employed plants of the same genus (Ephedra) as Ma Huang, and that the Hippuris of Dioscorides (about 50 A.D.) was E. fragilis var. graeca. The top of this plant was used as an astringent; taken with wine it was said to produce diuresis and to cure dysentery, and both root and top were reputed to be useful in the treatment of cough, orthopnea, and internal rupture (Berendes).
In Russia Ephedras have been in medical use since olden times. In the 19th century decoctions of E. vulgaris, together with milk and butter, were recommended in the treatment of rheumatism and were regarded as a specific remedy for syphilis and gout, the latter virtue being attributed to the twigs and roots of the plant. The sap and candied fruits were used in the treatment of respiratory disorders. A peasant named Kusmitsch effected such marvelous cures with decoctions of Ephedra that he won a wide reputation.

In India the dried branches of E. pachyclada, or E. intermedia, are thought to possess medicinal value, but they are chiefly used in religious (Parsi) ceremonials. It is also said that this plant, mixed with milk and honey and allowed to ferment, was the "soma" of the Vedas, which was used to induce an exhilarating intoxication. Incidentally, this appears to be the only instance of employment of an Ephedra for the purpose of pleasurable intoxication, and it is possible that the effects were due to alcohol in this case (see Chen and Schmidt, 1930).

In America a number of Ephedra plants were used by the Indians for various purposes. E. antisyphilitica, E. californica, and E. nevadensis were regarded as valuable in the treatment of syphilis and gonorrhea, and were used as local applications as well as by internal administration.
The Coahuila Indians made a cooling beverage from *E. nevadensis*, and the Panamint Indians made bread from the ground roasted seeds of the same plant. The Indians and Spaniards used decoctions of *E. californica* as a tonic and blood purifier, and *E. trifurca* was regarded as an excellent remedy for nephritis. In Mexico, *E. aspera* is still used occasionally in the treatment of pneumonia, and in Zacatecas *E. pedunculata* is highly esteemed as a remedy for pleurisy and pneumonia.

It appears, therefore, that the Ephedras have long been utilized as empirical remedies in many discontiguous parts of the world. On the whole, they seem to have enjoyed a reputation for two different sorts of usefulness—first, in the treatment of venereal diseases, and second, in treating disorders of the respiratory system.

The development of a useful modern drug out of these ancient remedies has centered upon the Chinese plant *Ma Huang* and, as is usually the case, has followed as a natural consequence of the isolation of an active principle. Pioneer work along these lines was done wholly by the Japanese, whose interest in Chinese drugs was naturally greater than that of the Western world because most of their empirical materia medica—including *Ma Huang*—was derived from the ancient culture of China. An active principle was first isolated from *Ma Huang* in 1885 by
G. Yamansashi, who obtained a crystalline though impure substance (cit Chen and Schmidt, 1950). After his death the study was continued by Nagai, with the assistance of Y. Hori, who obtained the alkaloid in pure form in 1887 (cit Chen and Schmidt, 1950). The same compound was obtained in Germany by E. Merck in 1888. The name ephedrine was first applied to this substance by Nagai, though the name had already been coined in 1875 by Loew (cit Chen and Schmidt, 1930) for the tannin which he had prepared from E. antisyphilistica. The name ephedrine is now used only in the sense in which Nagai employed it, viz., to designate an alkaloidal active principle of Ma Huang and other Ephedras.

Nagai's ephedrine was subjected to physiological investigations by Miura in 1887 (cit Chen and Schmidt, 1930). This study disclosed the toxic effects of large doses upon the circulation and demonstrated the mydriatic action of the drug. As a result it was introduced to Western medicine as a new mydriatic, but its vogue was limited and brief. Apparently it was not utilized for other purposes and was regarded as a very toxic substance. It is interesting to note that ephedrine, which by 1930 attained popularity as a substitute for or adjuvant to adrenaline was available in pure form five years before the actions of suprarenal extracts were first worked out.
completely and more than twelve years before adrenaline
the active p-rinciple of suprarenal medulla, was first
isolated.

Subsequently interest in ephedrine was, for many
years, almost wholly limited to analyses of its chemical
composition and to attempts at synthesizing it (see
below). The Japanese investigators Amatsu and Kubota
in 1917 (cit Chen and Schmidt, 1930) demonstrated the
essentially sympathomimetic effects of ephedrine, and
other workers – Hirose, and To – also contributed to the
same conclusion. These publications attracted little
attention in America and Europe, but as a result of
their work the Japanese became so convinced of the value
of ephedrine in the treatment of one condition that is
relieved by adrenaline namely, asthma – that an ephedrine
containing preparation was put on the market in Mukden
under the name of Asthmatol. No publication was made of
the results obtained with this product and when the
question of the therapeutic possibilities of ephedrine
was reopened in 1923 this development was unknown to the
Western world. It is proper, however, that the Japanese
scientists should be given due credit for having been the
first to appreciate the usefulness of ephedrine for
purposes other than ophthalmologic.

The work done by Chen and Schmidt who published
their results of first series of experiments in 1924
(Chen and Schmidt, 1924a and 1924b) upon this subject was the result of a suggestion made by a Chinese druggist, in response to an inquiry concerning native drugs which might be expected to possess real actions. Among others, Ma Huang was mentioned, and a small supply was obtained for future investigation. In the autumn of 1923 a decoction made from this material was injected into a vein of an anesthetized dog remaining alive at the end of a student exercise (cit Chen and Schmidt, 1930). The consequent circulatory effect was the one now familiar as that of ephedrine, and attention was concentrated upon this promising drug. A crystalline alkaloid was readily isolated from it, and further experiments demonstrated that this was the active principle, that it like possessed adrenaline/effects, that it was of comparatively low toxicity and that it was effectively absorbed from the gastro-intestinal tracts of dogs and men (Chen and Schmidt, 1924a and 1924b). A search of the literature disclosed the identity of this substance as ephedrine. Clinical trial of the drug was limited by the small quantity of ephedrine available at the time. As soon as a sufficient supply was prepared it was submitted to Dr. T.G. Miller, of the University of Pennsylvania, and to Dr. L.G. Rowntree, of the Mayo Clinic, for clinical experiments. The results being favourable, ephedrine was made available to clinicians in general, as rapidly as
possible. In 1926 ephedrine was submitted to the Council of Pharmacy and Chemistry of the American Medical Association, and was subsequently approved by it. (Chen and Schmidt, 1930).

One of the interesting aspects of the usefulness of ephedrine, as established by modern clinicians and experimenters, is that it justifies the Chinese tradition concerning Ma Huang in many respects (Chen & Schmidt, 1930).

Ephedrine occurs in certain plants of the genus Ephedra (family Ephedraceae) which includes a large number of species. These are distributed throughout the temperate and sub-tropical regions of Europe, Asia and America. They are found in an area extending from the middle Amur region through central Asia, including its deserts and covering China and Arabia, to the Mediterranean and even to the Canary Islands (Engler and Prantl), as well as Siberia, Hungary, the Carpathian Mountains, the Western Alps, and Western France. In the Americas they grow along the Rocky Mountains as far south as New Mexico, from Bolivia to Patagonia, and from Paraguay to the Atlantic Ocean.

Only a few of these Ephedras contain ephedrine. In China ephedrine-bearing plants are found in the Tai-hung Mountains, which are the site of the Great Wall
in Chihli Province. They also occur in Shansi, Shensi, Kansu, Honan, and Hupeh Provinces (Read and Liu, 1928). They are also found in Northern Chosen (Korea) and in Akita Prefecture in Japan. In India and Tibet they occur along the Himalaya Mountains (Chopra et al., 1928 and 1929).

The actual identification of Ma Huang has been somewhat uncertain. Cowdry (1922) identified Ma Huang as E. equisetina. Holmes (1926) suggested that Ma Huang is E. intermedia var. tibetica, while Stapf (1927) gave a provisional new name of E. sinica. Liu and Read (1929) identified another species, E. distachya, which is found in Western Chihli and is also known as Ma Huang. At present it appears that Ma Huang, from which most of the present supply of ephedrine is obtained, is E. sinica or E. equisetina (Small and Short). It has been shown by Chopra and his coworkers (1928), that ephedrine also occurs in the Indian species, E. vulgaris, E. pachyclada or intermedia, and E. intermedia var. helvetica. Their results have been confirmed by Read and Feng (1928).

These are the natural sources of ephedrine though ephedrine is also found in plants growing in Southern Europe, in Northern China and in Japan. Other Ephedras have been examined but they contained no alkaloid, or only the isomeric pseudoephedrine. The American species
E. trifurca, E. nevadensis, E. californica, and E. viridis were examined by Nielson, McCausland, and Spruth (1927), and found to contain no alkaloid. None of the American Ephedras have been shown to contain ephedrine, and upon transplanting the Swiss E. vulgaris (E. distachya), which is believed to yield ephedrine, no alkaloid was found in it after the first year of growth (Neilson and McCausland, 1928).

For laboratory and clinical uses the hydrochloride and sulphate derivatives are most commonly used. The hydrochloride appears as white odorless crystals, with a melting-point of 214-220°, is soluble in water and alcohol, insoluble in chloroform, ether, and paraffine oil. The sulphate occurs as fine, white, odorless crystals, melting at 240-245°C, soluble in water and hot alcohol, insoluble in ether, chloroform, and paraffine oil.

Probably the most important physical property of ephedrine is its stability. Ephedrine solutions are not decomposed by exposure to light, air or heat, and age apparently does not affect their activity.

Chen and Schmidt (1924a & 1924b) called the attention of the Western world to ephedrine in the belief that the actions of the drug were essentially sympathomimetic and that it should achieve a usefulness
similar to that of adrenaline. This belief has been strengthened by subsequent clinical experience, and appears to be amply justified. However, when the actions of ephedrine are compared with the pattern of sympathomimetic effects - i.e., the actions of adrenaline in the laboratory, many differences have been noticed between ephedrine and adrenaline. One important difference between adrenaline and ephedrine is that ephedrine crosses the blood brain barrier and produces the stimulation of the C.N.S. C.N.S. stimulation results in insomnia, nervousness, tremors and motor restlessness. Ephedrine stimulates the spinal cord and enhances spinal reflexes. In decapitated dogs, ephedrine facilitates the development of extreme degree of resistance to passive flexion of limbs (Hinsey et al, 1931). In spinal monkeys, ephedrine causes an increase in the excitability of spinal reflexes in acute preparations and hastens recovery from acute spinal shock (Jacobsen and Kennard, 1933). Ephedrine has got analgesic (pain relieving) action. Kiesing and Orzechowski (1941) demonstrated the ability of ephedrine to raise the pain threshold in dogs. Dews (1953) studied the action of ephedrine on spontaneous motor activity of the mouse. Low doses of ephedrine slightly increase the spontaneous motor activity. But doses higher than 125 mg/kg (upto
80 mg/kg) decrease the spontaneous motor activity. Another difference from adrenaline is that ephedrine can some what increase the strength of skeletal muscle power in patients suffering from myasthenia gravis. This effect was discovered accidently by Dr. Harriet Edgeworth, herself a victim of the disease, and in 1930 she described the results obtained in her own case. However, no such action is exerted on the skeletal muscles power of normal man. Thus, ephedrine was advocated as an adjuvant drug in the treatment of myasthenia gravis. But the action of ephedrine on the skeletal muscle power even in patients suffering from myasthenia gravis (a rare disease) is so mild that these days even its name is not mentioned among the drugs used in the treatment of myasthenia gravis (Taylor, 1980). These differences of ephedrine from adrenaline are due to its stability, oral availability and cap acity to reach certain organs which are not accessible to adrenaline.

The major difference which have been occupying the mind of various research workers is that on various preparations of different species of animals after denervation or after treatment with cocaine or after pretreatment with reserpine the actions of adrenaline and nor adrenaline are very much increased (supersensitivity)
where as the actions of ephedrine are very much decreased (subsensitivity) (see Singh and Garg, 1977).
To account for some of these differences Gaddum and Kwiatowski (1938) advanced the hypothesis that ephedrine acts by protecting the adrenergic mediator released from the sympathetic nerve endings as it inhibits the enzyme monoamine oxidase which destroys adrenaline (and noradrenaline) (see Gaddum, 1938).
There are many objections to this hypothesis. The main objections being that: (a) concentration of ephedrine capable of inhibiting the enzyme monoamine oxidase being too high to be achieved in human beings in the usual doses or even with the maximum dose which can be tolerated, (b) the enzyme monoamine oxidase destroys the adrenergic mediator inside the sympathetic nerve endings and once the adrenergic mediator is released it is destroyed by another enzyme known as catechol-o-methyl transferase. Thus, the hypothesis to explain the mechanism of action of ephedrine put forward by Gaddum and Kwiatowski (1938) could not stand the test of time. These days the acceptable hypothesis explaining the mode of action of ephedrine is the one put forward by Bron and Rand (see Burn and Rand, 1962). According to their hypothesis ephedrine like other indirectly acting sympathomimetic amines is taken up by the sympathetic nerve endings from where it displaces adrenergic mediator
which is released into the synaptic cleft. Thus, any procedure which would destroy the nerve endings (e.g. nerve degeneration after denervation) or prevent the uptake of ephedrine by the nerve endings (e.g. treatment with cocaine) or deplete the adrenergic mediator stored in the nerve endings (e.g. pretreatment with reserpine) is expected to abolish or reduce the actions of ephedrine.