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EPHEDRINE AND RELATED SUBSTANCES

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EPHEDRINE AND RELATED SUBSTANCES

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I. INTRODUCTION

The rise of ephedrine from obscurity to its present state of widespread popularity, within less than five years, involves a variety of features of unusual interest. Much of the initial enthusiasm for the

drug was doubtless due to the somewhat dramatic circumstance that the traditional faith of the Chinese in one of their ancient remedies was about to be justified by Western science. While ephedrine has recently found a real place in therapeutics, the drug was known to experimenters and clinicians for some thirty years before its possibilities were appreciated. The reason for this tardy recognition was simply the failure of the original investigators to use any but toxic doses in their animal experiments—a circumstance which illustrates the readiness with which an initial misconception may be propagated and may influence the subsequent fate of a new remedy. The history of ephedrine is therefore of more than usual interest.

Apart from the historical aspect, ephedrine has been the object of a great deal of investigation on the part of laboratory workers and clinicians. The result has been not only the discovery of unanticipated uses for the drug but—of greater ultimate importance—a renewal of interest in the problem of the relation of chemical composition to physiological actions, and the direction of attention to the incompleteness of our knowledge concerning the mode of action of sympathomimetic drugs (i.e , those which produce effects similar to the result of excitation of sympathetic innervations). It is now quite certain that ephedrine, in spite of its present popularity, is far from ideal in certain respects. In the search for other remedies of this sort important progress has already been made, and undoubtedly much more lies in the immediate future. For the benefit of those concerned in such work, and of the clinicians in whose hands rests the final decision concerning the validity of laboratory experimentation with agents of possible therapeutic importance, a compilation of the literature dealing with ephedrine should serve a useful purpose. For if ephedrine is not the only agent of this sort to have been introduced into therapeutics since epinephrine was discovered, it has certainly been the object of more investigation than any other. In spite of this, the literature is full of disagreements and unjustified assumptions with respect to the fundamental features in the action of the drug, though the clinical results are quite uniform in indicating that it produces effects that are of the same nature as those of epinephrine. It is inevitable that workers with other substances of this sort will be confronted with the same difficulties. These can be obviated, to some

extent at least, if it is generally realized that a drug can be sympathomimetic, in the original sense of the term, without duplicating all of the effects of epinephrine.

HISTORICAL

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 Pentsao 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, and Bechtin (1891) reported very striking results with decoctions of *E. vulgaris* in patients with rheumatism. Sassetsky and Lewaschew, however, were unable to confirm these results (Grahe).

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.

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 gonorrhoea, 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. Yamanashi, who obtained a crystalline though impure substance. After his death the study was continued by Nagai, with the assistance of Y. Hori, who obtained the alkaloid in pure form (1887). 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 for the tannin which he had prepared from *E. antisyphilitica*. 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 (1887). 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 has recently attained popularity as a substitute for or adjuvant to epinephrine, was available in pure form five years before the actions of suprarenal extracts were first worked out completely and more than twelve years before epinephrine, the active principle 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). Six years before our work was undertaken the Japanese investigators Amatsu and Kubota (1917) demonstrated the essentially sympathomimetic (epinephrine-like) 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 epinephrine—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 (and to the authors). 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 the authors 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. 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 possessed epinephrine-like effects, that it was of comparatively low toxicity, and that it was effectively absorbed from the gastro-intestinal tracts of dogs and men. 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 favorable, 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. The drug is now prepared by a number of manufacturers and is quite generally obtainable.

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.

II. PHARMACOGNOSY AND CHEMISTRY

1. Botany

Ephedrine occurs in certain plants of the genus *Ephedra* (family Ephedraceae) which includes a large number of species (35, according to Engler and Prantl, 1926; 45, according to the Index Kewensis, 1895–1920). These are distributed throughout the temperate and subtropical 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 associates, 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 and associates).

The actual identification of Ma Huang has been somewhat uncertain. It was formerly classified as *E. vulgaris* var. *helvetica* (Nagai; Botanical Nomenclature, etc.), but this name appears to be obsolete. Cowdry (1922) identified Ma Huang as *E. equisetina*, and this is the name recognized by the Council on Pharmacy and Chemistry of the American Medical Association for the plant from which ephedrine is obtained. Holmes (1926) suggested that Ma Huang is *E. intermedia* var. *tibetica*, while Stapf (1927) gave a provisional new name of *E. sinica* to specimens submitted by Read and by Parke, Davis & Company. Liu and Read (1929) identified another species, *E. distachya*, which is found in Western Chihli and is also known as Ma Huang. This statement needs confirmation. 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 recently 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 principal natural sources of ephedrine at present, 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, which is distinctly less useful than ephedrine. The American species *E. trifurca*, *E. nevadensis*, *E. californica*, and *E. viridis* were examined by Nielson, McCausland, and Spruth, and found to contain no alkaloid. Terry obtained the same negative result with *E. nevadensis*. Clark

and Groff reported the presence of pressor substances in extracts of *E. californica* and *E. nevadensis*, though no crystalline active substance could be isolated. Their results were not substantiated by De Eds and Butt or by Read and Feng. Black and Kelly found only pseudoephedrine in *E. alata*, collected in Morocco. 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, to this country, no alkaloid was found in it after the first year of growth (Nielson and McCausland, 1928).

2. Properties of ephedrine

a. Isolation. Ephedrine, having the solubility reactions of a typical alkaloid, is very easily separated from an extract of the plant. The following procedure has been found satisfactory.

The powdered crude drug is extracted with 60 per cent alcohol, the extract concentrated and treated with strong ammonum hydroxide or sodium carbonate. This causes precipitation, and filtration is necessary: ephedrine is present in both precipitate and filtrate, so that both must be dealt with. The akaloid is extracted from them by means of chloroform or ether. Upon removal of the solvent the residue is neutralized with dilute HCl or H_2SO_4, thus forming the corresponding salt of the alkaloid, which is finally purified and repeatedly crystallized from absolute alcohol. It is obvious that a chemical assay of ephedra-bearing plants is readily carried out, and this is fortunate because no satisfactory bio-assay has been developed.

b. Yield. Different investigators have obtained widely divergent results, even with the same plant, as shown in table 1. Generally speaking, the earlier workers obtained lower yields than the more recent ones, most of whom have succeeded in isolating more than 1 per cent of total alkaloids from the Chinese plants: of this 80 per cent or more is ephedrine. The Indian species *E. pachyclada* and *E. intermedia* var. *tibetica* have a distinctly lower ephedrine content than the Chinese.

Read and his associates in Peiping have made careful studies of this question. They (Feng and Read) find that the low yield of ephedrine obtained by previous workers was due to incomplete alkalinization of the percolate before extraction with chloroform or ether, and em-

phasize the necessity of adding a large excess of ammonium hydroxide in order to liberate the alkaloids completely. They have also studied the variations in yield of ephedrine from different parts of the plant and at different seasons of the year (Feng and Read, 1928). They find progressive increase in total ephedrine content from spring to autumn, the maximum being attained just before the frosts. The old Chinese custom of collecting the plant in the autumn therefore appears to be based upon sound observation. During the flowering season the male plant contains more alkaloid than the female, the

TABLE 1

Assay of Ephedras reported by different workers

SPECIES	TOTAL ALKALOIDS, PER CENT OF CRUDE DRUG	EPHEDRINE, PER CENT OF THE TOTAL	AUTHOR
Ma Huang	0 31–0 40		Nagai
Ma Huang	0 02–0 09		Chen
Ma Huang	0 30		Masucci and Suto
Ma Huang	0.40–0 86		Schoetzon and Needham
Ma Huang	0 20–0 90		Neilson, McCausland and Sprunt
Ma Huang	0 64–1 43		Williams
E. Equisetina	1 75	85–90	Feng and Read
B. Sinica	1 32	80–85	Feng and Read
E. vulgaris	1 02–1 27	50	Chopra, Dikshit and Pillai
E. vulgaris	1.65–1 70	70–80	Read and Feng
E pachyclada	1 8	30–36	Chopra, Dikshit and Pillai
E. pachyclada	1 15	30–40	Read and Feng
E. intermedia var. *Tibetica*	0.25–0 60		Chopra, Dikshit and Pillai

difference being greatest in May. After the fruiting season the alkaloid content is practically equal in plants of both sexes. With respect to the distribution of alkaloid in different parts of the plant, these investigators find (in *E. equisetina*) that the nodes contain much less ephedrine than the internodes, and that the root, berries, seeds, and woody stalks contain none at all. Similar conclusions were reached by Chopra and his associates with respect to Indian species of *Ephedra*.

The special tissue of the plant stem which is concerned in manufacturing or storing ephedrine has not been determined. Nothing is known about the manner in which it is synthesized by the plant or

the circumstances under which it may be transformed into its optical isomer, pseudoephedrine, or demethylated or methylated within the plant. A study of the climatic and soil conditions under which the plant would produce its maximum yield of ephedrine could be made with profit.

c. Recent commercial development. The recent popularity of ephedrine has led to the development of a considerable industry in China. Ephedrine has been upon the market for more than 30 years. It has been listed in E. Merck's Index since 1896. Japanese manufacturers (Dainihon Seiyaku Kabushiki Kaisha, of Osaka, later succeeded by the firms of Tanabe and Takeda) also prepared ephedrine, and the proprietary preparation Asthmatol contained ephedrine. As far as is known to the reviewers, these were the only commercial supplies of ephedrine in the world prior to 1924, and the quantities produced were relatively insignificant, since the drug was scarcely used at all except for chemical investigations. According to Mr. G. Woodard, Assistant Trade Commissioner of the United States at Shanghai, Ma Huang was exported almost exclusively through German firms for the past 30 years. Read (1928) states that Ma Huang was probably never exported from Tientsin prior to August, 1926, but from this time the trade developed rapidly. By the end of 1926 the exports from Tientsin alone, and to the United States alone, amounted to 224,058 pounds, valued at $17,753, during 1927 they were 622,060 pounds and $64,840, and for the first 11 months of 1928 they were 1,003,700 pounds and $69,300. (The figures for 1926 and 1927 are cited by Read; those for 1928 were furnished by Mr. A. G. Ward, U. S. Vice-Consul at Tientsin.) In addition to the crude drug, ephedrine hydrochloride, prepared by the Department of Chemical Products of Peiping Union Medical College, was exported through Tientsin as follows: in 1926, 12½ pounds, valued at U. S. $3,612; in 1927, 23 pounds and $7,490; in 1928 (to December 1) 20 pounds and $3,688. Ma Huang has also been exported from Shanghai and Hankow, but the quantities concerned are unknown to the writers: it is certain that the above figures underestimate the Chinese trade in this drug. Furthermore, ephedrine-containing plants are also exported from Osaka and Tokyo, Japan, and from Karachi and Rawalpindi, India. The world supply of these plants appears to have

satisfied the demand during 1927, and is now greater, for the average price of Ma Huang shipped from Tientsin to the United States during 1927 was U. S. $10.43 per 100 pounds, while during 1928 it fell to $6.91.

In contrast with the two concerns—one German, one Japanese—who were the sole purveyors of pure ephedrine prior to 1924, the drug is now being prepared by eight firms in the United States, by one in Canada, by three in England, by two in Germany, by three in China, by four Japanese companies, and by two in India. There may be others of which the writers are unaware.

d. Physical and chemical characteristics. The alkaloid ephedrine is deposited from an ether solution as an oily substance, but colorless and odorless crystals appear as needles or rosettes on standing or recrystallization. These melt at 34–40°C. and boil above 200°C. The specific rotation, $[\alpha]_D^{20}$, of the base is between $-6°$ and $-7.5°$. The alkaloid is soluble in ether, chloroform, alcohol, petroleum ether, and water, the solutions being strongly alkaline to litmus paper. The crystallography of ephedrine has been investigated by Schwankte, and Walcott (quoted by Peterson, 1928). Geppert investigated its effects upon the surface tension of water. A peculiar reaction of ephedrine is the formation of the hydrochloride when it is shaken with chloroform: this was pointed out by Peterson (1928), and is responsible for the high melting point incorrectly reported by Chen (1925) for ephedrine base.

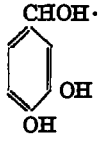
For laboratory and clinical uses the hydrochloride and sulphate derivatives are most commonly used. The hydrochloride appears as white odorless crystals, with a melting-point of 214–220°, $[\alpha]_D^{20}$ $-33°$ to $-35.5°$; it contains 17.3 to 17.7 per cent of C^-, is soluble in water and alcohol, insoluble in chloroform, ether, and paraffine oil. The sulphate occurs as fine, white, odorless crystals, melting at 240–243°C. $[\alpha]_D^{20}$ $-29°$ to $-30°$, containing 21.8 to 23.1 per cent of SO_4^{--}, soluble in water and hot alcohol, insoluble in ether, chloroform, and paraffine oil.

Solutions of ephedrine or its salts react with few of the alkaloidal reagents. With Mayer's reagent there is a turbidity or white precipitate, according to the degree of concentration. Tsiang and Brown (1927) described characteristic micro-crystalline reactions when

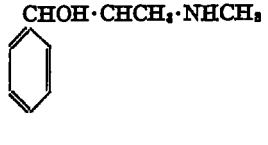
ephedrine is treated with Millon's reagent, gold chloride, platinic chloride, or Kraut's reagent. The most serviceable qualitative reaction of ephedrine is that with copper sulphate and sodium hydroxide, which was first pointed out by Nagai (1892): a purple color appears, which is extractible with ether. This test is sensitive to one part of ephedrine in 400, and if the concentration exceeds 1 in 40 a pinkish purple precipitate is formed, and this is completely soluble in ether.

The chemical behavior of ephedrine has been exhaustively studied by E. Schmidt, Nagai, E. R. Miller, Flaecher, Calliess, Emde, and others. Probably the most important property is its stability: ephedrine solutions are not decomposed by exposure to light, air, or heat, and age apparently does not affect their activity. Thus, a solution of ephedrine hydrochloride, prepared and sealed in a sterile ampule by the authors on December 23, 1923, showed no change in appearance when opened on March 14, 1929, and produced the customary pressor response when injected into a pithed cat. Kendall and Witzmann (1927) have demonstrated the great resistance of ephedrine to oxidation, as compared with epinephrine: the former is not oxidized by dibromphenolindophenol, naphtholdichlorindophenol, methylene blue, or indigo carmine, while the latter is oxidized by all these agents.

e. Structure and isomerism. The chemical constitution of ephedrine has been studied by Ladenburg and Oelschlägel, Nagai, E. Merck, E. Schmidt, E. R. Miller, Rabe, Ogata, and others. The empirical formula has been definitely established as $C_{10}H_{15}ON$, the structural formula as $C_6H_5 \cdot CHOH \cdot CHCH_3 \cdot NHCH_3$, or β-phenyl-β-hydroxy-α-methyl-ethyl-methyl amine, or 1-phenyl-2-methylaminopropanol-1, or α-hydroxy-β-methylamino-propyl benzene:



Epinephrine



Ephedrine

Its chemical similarity to epinephrine is obvious.

The above graphic formula of ephedrine contains two asymmetric carbon atoms, so that two sets of stereoisomers, making six in all, are

possible. All have been prepared synthetically (see the following section); they are designated *l*-, *d*-, and *dl*-ephedrines, *d*-, *l*-, and *dl*-pseudoephedrines, the *dl* forms being optically inactive racemic mixtures. Only two occur in nature, namely *l*-ephedrine, which is the ephedrine now in use, and *d*-pseudoephedrine, which is also found in Ma Huang, and which is the pseudoephedrine first isolated by Merck from European *Ephedra*, and recently prepared by Chou and Read (1926) from Ma Huang extracts from which ephedrine had been removed. This is the pseudoephedrine of current literature. Pseudoephedrine is quite unlike ephedrine in melting-point (118°C.), optical rotation ($[\alpha]_D^{20}$ + 50°) and, to a certain extent, in physiological effects. It is of particular interest, however, because ephedrine can readily be converted into it under certain conditions, which were studied by E. Schmidt, Nagai, and Calliess, more recently by Chou (1926). The literature dealing with the isomerism of these alkaloids was reviewed by Chen and Kao (1926). Emde (1928) has obtained evidence that the —OH and —$NHCH_3$ groups are distant from each other in the ephedrine molecule but close together in the pseudoephedrine molecule.

f. Other alkaloids occurring in Ma Huang. In addition to ephedrine and pseudoephedrine, three other related (but not isomeric) alkaloids have been isolated from Ma Huang. Smith (1927, 1928) obtained *l*-methyl-ephedrine and nor-*d*-pseudoephedrine. Nagai and Kanao (1928) confirmed these findings, and succeeded in isolating a third alkaloid, namely, *d*-methyl-pseudoephedrine. It appears therefore, that ephedrine, like several useful alkaloids, occurs in nature along with closely related substances, though of these only pseudoephedrine occurs in appreciable quantity.

g. Synthesis of ephedrine. E. Schmidt and his associates made various attempts and advances toward the synthesis of ephedrine. Fourneau (1904) prepared a compound having the formula of ephedrine. He and his associates later succeeded in the synthesis by different methods. His process was patented in England (1927). Nagai accomplished the synthesis in 1911 and patented his product in Japan, the United States, Canada and England, under the name of *Methylmydriatine*. All these products were racemic, as is always the case when an optically active substance is synthesized. However,

according to Ogata (1919), Nagai succeeded in 1918 in resolving his product into *l*- and *d*-ephedrines. Recently, Nagai (1927) has stated that he was able to synthesize two racemic ephedrines, one melting at 40°, the other at 70°, and in separating each into its *d*- and *l*-components by means of tartaric acid: the pair obtained from the mixture melting at 70° he called isoephedrines (identical with pseudoephedrines). Späth and Göhring (1920) described their complete success in the synthesis and separation of all six isomers. Eberhard (1915) also succeeded in synthesizing racemic ephedrine. Kanao (1927) reported the success of his attempts to synthesize and separate the six isomers, confirming the results of Späth and Göhring. E. Merck has recently placed synthetic racemic ephedrine on the market, under the name of *Ephetonin;* the process of preparation is patented in Germany and England. Manske and Johnson (1929) and Skita and Keil (1929) have recently achieved new syntheses of ephedrine. Fourneau and Nicolitch, Manske and Johnson, and Neuberg, Jacobson and Wagner employed chemical agents other than tartaric acid in the resolution of racemic ephedrine.

It is obvious that the final confirmation of the deduced structure of ephedrine—namely, synthesis of the substance—has been furnished repeatedly. At present the natural product is more widely used than the synthetic and at the time of writing American manufacturers are supplying only natural ephedrine.

III. PHARMACOLOGICAL ACTION

Chen and Schmidt (1924) 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 epinephrine. 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 epinephrine—in the laboratory, differences are perhaps more frequent than analogies, and there has recently been a tendency on the part of several investigators to emphasize the differences as indicative of an absence of any sympathomimetic effect on the part of ephedrine. It is scarcely to be expected, of course, that two different substances, however closely

related, would possess physiological effects that are identical in all respects, but if it should be proved that the important actions of ephedrine are fundamentally different from those of epinephrine the present attitude of physicians toward ephedrine would have to be radically altered. On the whole, there appears to be no conclusive evidence that the actions of ephedrine that are of therapeutic importance are not sympathomimetic, and there is considerable evidence that they are. On the other hand, there is scarcely any respect in which the effects of ephedrine are identical with those of epinephrine, and there are several instances in which the two substances have opposite actions upon the same structure or function.

1. Action on lower forms of life

Very little work has been done along these lines. Macht (1929), who has made a systematic study of the toxic effects of various substances upon living plant organisms found that ephedrine was much less toxic than epinephrine to the seedlings of *Lupinus Albus*, a concentration of 1 in 5,000 of ephedrine having a phyto-toxic index of 75 per cent. This is in accord with other observations of the same author, indicating that a drug of animal origin is more toxic to plants than one of vegetable origin. In the sea crab, *Palaemon*, kept in 1 to 1000 solution of ephedrine, a temperature of 36° induces heat narcosis in 30 minutes (Fröhlich and Kreidl, 1921).

Nadler reported interesting results from experiments with the squid (*Loligo pealii*). He found that epinephrine and ephedrine, injected subcutaneously, produced local blanching, which was supposedly due to inhibition of smooth muscle of the chromatophore system. The effect of ephedrine differed from that of epinephrine in two respects, however. First, the blanching was much slower in its appearance when ephedrine was used, though it lasted 8 hours or more instead of 10 minutes, which was the duration of the epinephrine effect. Second, the animals injected with ephedrine showed a diffuse generalized reddish coloration excepting at the injected area; this coloration was also produced by intravascular or oral administration of the drug. Since excitement or irritation of the animal likewise caused the same color change, it was ascribed to stimulation by ephedrine of the central nervous system of the animal; epinephrine

apparently had no such effect. These results indicate that the action of ephedrine upon this animal is twofold: a peripheral epinephrine-like one, and a stimulant one on the central nervous system.

Nadler also found that a number of substances produced peripheral effects opposite to those of epinephrine and ephedrine, namely, a local deep coloration at the site of injection. These were parathyroid and anterior pituitary extracts, posterior pituitary extract, and barium chloride. The last two are known to stimulate smooth muscle fibers directly, irrespective of their innervation (i.e., they are musculotropic), and the effects in the squid were thought to be due to contraction of the chromatophore musculature. He found that epinephrine or ephedrine, injected in sufficient quantity into the red zone produced by injection of any of these agents, was able to antagonize the effect and produce local blanching.

This is the only investigation, upon one of the lower forms of life, of the fundamental nature of the action of ephedrine. The conclusion was that the action of ephedrine is epinephrine-like (sympathomimetic) and not pituitrin-like (musculotropic).

2. Actions on the circulation

These are probably the most striking effects of ephedrine in the common laboratory animals, and it is somewhat strange that they were not investigated until comparatively recent times. If they had been, the present status of ephedrine might have been attained several decades ago.

a. The effect upon blood pressure. The first work—that of Miura (1887)—led to the conclusion that ephedrine is essentially a circulatory depressant. The doses used by him were excessive (fatal) ones, and cardiac depression evidently dominated the picture. Grahe (1895) reported a slight rise of blood pressure of curarized dogs upon subcutaneous or intravenous injection of ephedrine or pseudoephedrine, but his published tracings show barely detectable effects. He also found that subsequent injections led to a fall in pressure. The first demonstration of the characteristic pressor effect of ephedrine was that of Hirose (1915), who injected the drug intravenously in anesthetized rabbits. Amatsu and Kubota (1917) confirmed these results, and added the observation that the rise in pressure was not prevented by

destruction of the medulla or by paralytic doses of chloral hydrate. Chen and Schmidt (1924) demonstrated similar effects in cats and dogs, and emphasized the relatively long duration of the effect of ephedrine, the diminution, disappearance, or reversal of the effect upon repeated injections, and the ability of ephedrine to raise blood pressure when taken by mouth. Since then many workers have contributed to the subject, and the principal features in the circulatory actions of ephedrine are well established.

Ephedrine causes a rise in blood pressure of anesthetized dogs when injected intravenously in dosage of 0.005 to 30 mgm. per kilogram, but the greatest effect is produced by doses of 1 to 10 mgm. per kilogram: following such injection, blood pressure rises by 100 or more millimeters of mercury and is maintained at this level for at least 15 to 25 minutes. In unanesthetized dogs, 5 to 10 mgm. of ephedrine per kilogram, by vein, was found by Pennetti (1928) to cause a rise in pressure lasting 3 to 4 hours.

The pressor effect of ephedrine appears to be less marked in rabbits than in cats and dogs (Kreitmair, 1927). The minimum pressor dose, injected intravenously, was found to be 0.05 mgm. per kilogram in rabbits, while 1/50th of this quantity was effective in cats.

Large quantities of ephedrine (40 to 65 mgm. per kilogram) injected intravenously in dogs, cause only a fall in blood pressure (Chen and Meek, 1926): these are close to the fatal dose. Kreitmair (1927) states that 10 mgm. or more per kilogram injected into a vein causes a fall in blood pressure in cats. This is the type of effect observed by Miura (1887), who apparently did not try smaller doses.

When the pressor effect of ephedrine is compared with that of epinephrine, several outstanding points of difference are apparent. First, the effect of epinephrine is much more intense but much less prolonged than that of ephedrine: under optimal conditions, employing intravenous injections in cats, the rise in pressure produced by epinephrine is 100 (Nagel, 1925) to 142 (Chen) times as intense as that of the same quantity of ephedrine, but the effect of ephedrine commonly persists 7 to 10 times as long as that of epinephrine (Chen). Second, the intensity of effect of epinephrine is so closely proportional to the quantity injected that the pressor response can be employed in assaying epinephrine preparations (United States Pharmacopoeia,

Ninth Revision); this is distinctly not the case with ephedrine, the circulatory effects of which are by no means proportional to the quantity injected (Chen and Schmidt, 1924); they may be less from large doses than from smaller ones. Third, following an intravenous injection of epinephrine blood pressure frequently falls from the peak of the pressor effect to a subnormal level, rising slowly to normal; this is not true of ephedrine, following which pressure simply falls very gradually to normal (Kreitmair, 1927). Fourth, when epinephrine injections are repeated the same degree of effect will be obtained from each; with ephedrine, however, the first dose is by far the most effective one, and upon repetition the pressor effect of each becomes progressively less until it disappears completely or is replaced by a depressor effect (Chen and Schmidt, 1924). This latter feature has been noted repeatedly (Rowe, 1927; Rudolf and Graham, 1927; Kreitmair, 1927; Pittinger, 1928; Launoy and Nicolle, 1928) in cats, dogs, and rabbits, anesthetized or pithed. Its explanation involves factors which are also responsible for most, if not all, of the other differences between the circulatory effects of ephedrine and epinephrine, and the observations bearing upon this question may properly be considered at this time.

The extent to which the circulation becomes "tolerant" to repeated injections of ephedrine has been found to depend upon the size of the dose. Thus, comparatively large quantities (about 5 mgm. per kilogram), injected rapidly and at frequent intervals (5 to 10 minutes) very quickly become ineffective and soon lead to a depressor effect from each injection. On the other hand, small doses (0.02 to 0.05 mgm. per kilogram) may show cumulative effects (i.e., a step-like rise in pressure to a sustained high level) if injected at close intervals (Chen, 1926), and if time is allowed for pressure to recover between injections each may sometimes—though by no means always—produce the same pressor effect. The explanation advanced (Chen and Schmidt, 1924) for the decreasing effectiveness of repeated injections of ephedrine is that maximal pressor effects are soon developed, and that additional quantities of the drug are then incapable of producing further stimulant effects. It has been suggested (Chen and Meek, 1926) that the "receptors" with which ephedrine combines may be fewer in number, or more easily saturated, than those of

epinephrine, which would account for the absence of progressive effects as the dose of ephedrine is increased above the optimum level. It seems probable that the greater persistence of ephedrine actions depends upon a more stable union with receptor substance than is the case with epinephrine and if the ephedrine receptors are saturated early the lack of progressive effect from repeated injections of ephedrine is accounted for. When the quantities of ephedrine are small this saturation would not be accomplished until a number of injections have been made. Such explanation appears to harmonize with experimental observations, and is the best available at present; it is, of course, purely hypothetical.

The depressor effect of ephedrine was attributed by Chen and Schmidt (1924) to cardiac depression—an effect which is well known and will be considered in the following section. It is wholly unlike the depressor action of epinephrine, which can be demonstrated with minimal doses and is apparently due to stimulation of vasodilator nerve endings (Dale: Journ. Physiol., 1906, xxxiv, 163): with ephedrine, a first injection is always purely pressor unless it is very large; a depressor effect from a small or moderate dose can be demonstrated only after maximal pressor effects have been produced by previous injections, and there is no evidence that any dose of ephedrine can produce a vasodilator effect comparable with that of epinephrine. The fact that the pressor effect of epinephrine is often followed by a depressor (vasodilator) one, while that of ephedrine is simply followed by recovery to normal, also indicates that the ability to stimulate vasodilators is either lacking completely in ephedrine, or is very much less conspicuous than is the case with epinephrine. It may be noted also that the pressor action of ephedrine is more affected by the condition of the subject than is the case with epinephrine. Animals whose blood pressures have been lowered by trauma, operative procedures, hemorrhage, etc., show much less pressor effect than normals, and are more likely to show only a fall in pressure following a moderate dose of ephedrine (Chen, 1925). Deep anesthesia and consequent hypotension also increase the probability of fall in pressure after only a few injections of ephedrine (Chen, 1925). Under such circumstances increasing the dose of ephedrine would be more likely to lead to fall than to rise in blood pressure—a contingency that is not encountered with epinephrine.

In brief, it appears that the capacity of ephedrine to raise blood pressure is limited by two factors: first, by its relative weakness as a circulatory stimulant, perhaps because there are only relatively few "receptors" with which it can combine, and additional quantities of the drug are incapable of producing further effects once these have been saturated; second, by the depressant action of ephedrine upon the heart—an effect that is masked by the pressor effect until the latter has become maximal, or unless overwhelming quantities are injected. Epinephrine is not subject to these limitations to anything like the same degree as ephedrine. This suggests that a mixture of the two drugs might possess the virtues of both—the intensity of epinephrine and the persistence of ephedrine—while minimizing their respective disadvantages—the evanescence of epinephrine and the danger of cardiac depression by ephedrine. This has actually been found to be the case.

Thus, Chen and Meek (1926) found that upon intravenous injection of ephedrine and epinephrine in dogs there was summation, both in intensity and duration, of the pressor effect. Launoy and Nicolle (1928) report an actual potentiation when such injections are made in unanesthetized rabbits, the rise in pressure being greater than the sum of the effects of both drugs given separately. Csépai and Doles-shall (1928) found that ephedrine sensitizes the human circulation to intravenous injections of epinephrine, the influence being especially marked in cases of hyperthyroidism; they believe that ephedrine sensitizes sympathetic nerve endings just as thyroxin sensitizes the cells to the action of hormones.

The action of ephedrine upon the human blood pressure has now been studied extensively, and with quite uniform results. The first study was that of Miller (1925), who reported rise in pressure in 70 out of 84 individuals given a dose of 50 to 125 mgm. of ephedrine orally or by subcutaneous injection. In 7 cases pressure was not altered, while in 6 it fell. The rise in pressure varied from a few millimeters to 65, and its duration was 6 to 8 hours. Similar results were reported by Rowntree and Brown (1926), Pollak and Robitschak (1926), Rudolf and Graham (1927), Hess (1926), Jansen (1926), Kesten (1927), Middleton and Chen (1927), Althausen and Schu-macher (1927), Wu and Read (1927), Csépai and Fernbach (1928),

Radoslav and Stoïcesco (1927), and Pennetti (1928). Anderson and Homan (1927) observed a rise in pressure in children given 15 mgm. of ephedrine hydrochloride. The results of Rowntree and Brown (1926), and of Hess (1926), indicate that blood pressure can be maintained at an elevated level for several days by means of daily administration of ephedrine. All observers agree that ephedrine is effectively absorbed following oral administration, and Hess (1926) has shown that rise in blood pressure also occurs following rectal administration of ephedrine, in dosage of 2 mgm. per kilogram, as suppository, in milk, or dissolved in the proctoclysis fluid. Intravenous injection was first tried by Miller (1925), subsequently by Jansen (1926). The effects are more marked than those of other routes of administration, but last only 15 to 30 minutes (Jansen).

The influence of disease upon the pressor effect of ephedrine in man has been studied by several workers. In Graves' disease, in which there is conspicuous sensitization to epinephrine, Pollak and Robitschek (1926) reported unusually marked pressor effects from ephedrine, but Csépai and Fernbach (1928) concluded that there is no sensitization to ephedrine in Graves' disease. In asthma, Thomas (1926) and MacDermot (1926) found no rise in pressure following oral administration of ephedrine, and a similar statement was made in an earlier review by Chen and Schmidt (1926). However, studies of larger series of cases by Althausen and Schumacher (1927) and Middleton and Chen (1927) have shown that ephedrine raises blood pressure in asthmatic patients, possibly less frequently than in normals, but to as high a level and for as long a time. Pennetti (1928) tried ephedrine in a single case of myxedema and found a fall in blood pressure from 210 to 145 mm. of mercury.

The effect of repeated doses of ephedrine, taken by mouth, upon the blood pressure of human beings has been investigated by Rowntree and Brown (1926) and by Chen (1928). It appears that when a therapeutic dose (50 mgm.) is taken by mouth every two to three hours the first causes the most marked rise in pressure, the subsequent ones causing further but smaller rises in the already elevated pressure and maintaining it at an abnormally high level as long as the drug is given regularly. These results are therefore similar to those obtained by intravenous injections of small doses (0.02 to 0.05 mgm. per

kilogram) at short intervals in anesthetized dogs, and appear to indicate that the pressor effect of such dosage is not nearly maximal. The circulatory effect of a single dose of ephedrine, taken by mouth, evidently disappears completely within 14 to 24 hours, a second dose of the same size then producing practically the same effect as the first (Chen, 1928).

The effect of ephedrine upon venous pressure was studied by Chen and Meek (1926) in two dogs, one of which was atropinized. In each, a slight fall in venous pressure coincided with the rise in arterial pressure.

b. The action on the heart. The first investigations of the physiological effects of ephedrine disclosed its power of depressing the heart. Miura (1887) observed that lethal doses of ephedrine caused diastolic arrest of the frog's heart. Grahe (1895) found that ephedrine or pseudoephedrine, applied to the frog's heart by irrigation or injected intravenously, caused depression and irregularities, and that a heart arrested by either drug could not be made to beat by means of atropine, though a heart arrested by muscarine could be made to beat when treated with ephedrine or pseudoephedrine. Amatsu and Kubota (1917) obtained similar results with frog's heart studied by Engelman's and Straub's methods, confirming the inability of atropine (as well as camphor) to overcome the depressant effect of ephedrine. Chen and Schmidt (1924) found only depression of the frog's heart irrigated with ephedrine.

Subsequent investigations have confirmed the conclusion that ephedrine is essentially depressant to the frog's heart, while showing in addition that small quantities may exert an inconspicuous stimulant effect. Chen and Meek (1926) found that ephedrine sulphate, applied to the heart in concentration of 1 in 1,000, may cause acceleration by a few beats per minute, but a 1 in 100 solution was purely depressant to rate and amplitude. Barlow and Sollmann (1926), who perfused the heart by the method of Howell and Cooke, found pure depression with concentrations of ephedrine sulphate of 1 in 10^5 or stronger, rate, force and output being diminished, and with 1 in 10^8 dilutions complete heartblock was elicited; stimulation was occasionally observed with dilutions of the order of 1 in 10^7, being manifested as an increase in rate and amplitude, but the increase

rarely exceeded 10 per cent. Kreitmair (1927) noted increase in amplitude of the frog's heart perfused by Straub's method with 1 in 10^4 ephedrine hydrochloride; rate was not affected, and higher concentrations were purely depressant, 1 in 100 causing arrest that could be combated by means of perfusion with 1 in 10^4 dilution of epinephrine, with calcium, or with histamine, but was not reversible upon simple perfusion with pure Ringer's solution, and was not affected by atropine. Gradinesco (1927) also found that epinephrine is able to restore the beat to the frog's heart arrested by perfusion with ephedrine. Gomes da Costa (1927) reported stimulant effects of dilute solutions of ephedrine upon the perfused frog's heart, but Lévy and Boyer (1927) found only depression when any effect was evident. Méhes and Kokas (1929) likewise observed depression of the frog's heart perfused with a 1 in 50,000 dilution of ephedrine, and believed that the effect was partly removed by small quantities of atropine.

The hearts of certain invertebrates have also been studied with respect to the effects of ephedrine. Lévy and Boyer (1927) studied the heart of the snail (*Helix pomatia*) and found systolic contracture with a 1 in 20 solution of ephedrine; weaker solutions (1 in 100, 1 in 1,000) caused a slowing in rate and an increase in strength of contraction, with periodic variations. Bain (1929) perfused the hearts of crabs (*Maia squinado*, *Cancer pogurus*, and *Carcinus moenas*) with ephedrine, among other drugs, including epinephrine which, in 1 to 50,000 dilution caused a marked increase in rate and tone of the hearts: ephedrine was used in the same dilution as epinephrine, and produced no effect whatever. Apparently a stronger solution of ephedrine was not used, so that one can conclude only that ephedrine is weaker than epinephrine in its effects upon these hearts, as upon all others.

The isolated heart of the toad was perfused with ephedrine and pseudoephedrine by Loo and Read (1928): they usually found depression of amplitude of beats with 1 in 20,000 ephedrine following pseudoephedrine but ocasionally ephedrine caused acceleration.

The turtle's heart was perfused with ephedrine by Chen and Meek (1926): dilutions of 1 in 10,000 sometimes accelerated the rate slightly, but 1 in 1,000 or 1 in 100 caused bradycardia, usually with decrease in amplitude, culminating in diastolic arrest.

The action of ephedrine on the mammalian heart was investigated by Chen and Schmidt (1924) and by Chen and Meek (1926). Pulse rate in the intact unanesthetized dog is usually slowed, occasionally accelerated, when ephedrine is injected subcutaneously or intravenously; in the anesthetized animal acceleration is commonly observed following intravenous injection of less than 1 mgm. per kilogram, though after larger doses (1 to 20 mgm. per kilogram) slowing is commonly seen. Atropine completely abolishes or prevents the bradycardia, which is thus to be regarded as a reflex effect of the rise in blood pressure, the slowing being greater in animals whose cardio-inhibitory centers are not depressed by anesthesia. This explanation is, however, called into question by the recent experiments of Pennetti (1928), who found that section of the vagi or injection of atropine in unanesthetized dogs does not usually accelerate the heart slowed by ephedrine. Confirmation of these results is highly desirable. Coelho (1929) reports that in dogs narcotized with chloralose, ephedrine, in dosage of 1 to 20 mgm. per kilogram, causes acceleration of the heart.

The strength of the beats of mammalian hearts has also been found to be increased by ephedrine. Chen and Schmidt (1924) recorded the contractions of part of the right ventricle (myocardiograph) and found them markedly increased by ephedrine. The effect was not prevented by section of the vagus nerves or by atropine, was not due to an atropine-like effect upon cardio-inhibitory nerves, and was fully comparable with that of electrical stimulation of the accelerator nerve or of injection of epinephrine. They also showed that ephedrine caused increase in rate and amplitude of ventricular contractions when applied locally to the stellate ganglia—a feature in action that is not shared by epinephrine (Chen and Meek, 1926). Intravenous injection of ephedrine caused still further acceleration and augmentation. Large quantities of ephedrine (40 to 55 mgm. per kilogram by vein) are apt to cause acute cardiac depression (Chen and Meek, 1926). The cardiac stimulant action of small quantities of ephedrine and the depressant action of large quantities have also been observed by Kreitmair (1927) on cats and by Launoy and Nicolle (1928) on rabbits. Chopra, Dikshit, and Pillai (1929) found increase in auricular contractions in cats given 2 mgm. injections, the ventricles being unaffected, while with 5 mgm. both auricles and ventricles were depressed.

It has been shown by La Barre (1928) that ephedrine does not lead to ventricular fibrillation in cats under chloroform anesthesia; in this respect ephedrine differs from epinephrine.

Studies of the effect of ephedrine upon the cardiac output of dogs were made by Chen and Meek (1926) by means of cardiometric and teleoroentgenographic methods. They concluded that in the (anesthetized, atropinized) dog there is a distinct and constant increase in volume output per minute at the time of increase in pulse rate and rise in blood pressure. Wilson, Pilcher, and Harrison (1928) employed the Fick principle to measure cardiac output of unanesthetized dogs, and found that ephedrine caused an increase in minute volume, especially when the drug was given subcutaneously or by mouth. Halsey, Reynolds, and Blackberg (1927) employed the same methods but obtained opposite results, i.e., ephedrine was found to decrease the cardiac output of unanesthetized dogs as well as of dogs narcotized with chloroform or chloral hydrate. It should be noted that results obtained by this procedure are frequently opposed to those obtained by other methods. For example, digitalis, which has been universally regarded as a stimulant to cardiac muscle and is found to be such by other methods of investigation, decreases cardiac output as measured by the Fick method and appears to be essentially a cardiac sedative (Harrison and Leonard: Jour. Clin. Invest., 1926, iii, 1); and quinidine and chloral hydrate, which, by other methods of investigation, are shown to be marked cardiac depressants, appear as cardiac stimulants according to the results obtained by this method (Halsey, Reynolds, and Blackberg, 1927). Until such discrepancies are satisfactorily explained it is impossible to evaluate the results obtained with respect to ephedrine.

Electrocardiographic studies made by Chen and Meek (1926) in unanesthetized and anesthetized animals, showed that small doses (5 to 10 mgm. per kilogram by vein in dogs) did not alter the contour of the curve, apart from the T-wave, which might be flattened, inverted, or occasionally augmented. Massive doses (40 to 75 mgm. per kilogram), given intravenously to dogs and rabbits, appeared to depress the automatic and conducting systems in descending order, that is, from sino-auricular node to the ventricular terminations of the Purkinje system: there were, in the order of their appearance, brady-

cardia, prolongation of the P-R interval, partial auriculo-ventricular block, nodal rhythm, ventricular automatism or extrasystoles, bundle branch block, finally ventricular fibrillation. Similar results were obtained by Coelho (1928) in dogs narcotized with chloralose.

The isolated mammalian heart has also been studied: Chen and Schmidt (1924) and Chen and Meek (1926) found that the rabbit's heart perfused according to Langendorff's method was stimulated in rate and strength of beats by low concentrations (1 in 100,000) of ephedrine sulphate, while stronger solutions (1 in 10,000, 1 in 5,000) caused depression of both rate and strength; still stronger solutions (1 in 2,000) brought about partial block, and 1 in 1,000 caused prompt failure (Chen and Meek, 1926). Similar results were obtained by Chopra, Dikshit, and Pillai (1929), and by Pennetti (1928); the latter found that epinephrine was able to revive a heart arrested by ephedrine.

The effects of ephedrine upon the human heart have received considerable study. The effect upon pulse rate was observed by Chen and Schmidt (1924) in a small series of cases, all of whom showed a slowing after oral or subcutaneous administration of ephedrine. Miller (1925), in a much larger series, found slowing of the pulse during the rise in blood pressure in the majority, but in 16 of his 84 subjects pulse rate was accelerated by ephedrine. Pulse rate and blood pressure returned to normal at about the same time. Rowntree and Brown (1926) noted acceleration of the pulse as frequently as slowing, and Middleton and Chen (1927) observed that acceleration was produced more frequently than slowing. In the experience of Hess (1926) and of Rudolf and Graham (1927), a decrease in pulse rate was the more frequent result of ephedrine, but in the cases of Jensen (1926) acceleration was the more frequent. In some cases in all these series pulse rate was unaffected. On the whole, the effect of ephedrine upon the rate of the human heart appears to be of the same nature as that upon the dog's heart, namely, acceleration or slowing, depending upon conditions which are not well understood. The influence of atropine upon the cardiac effects of ephedrine in man has apparently not been investigated, but it may be inferred that bradycardia following a therapeutic dose of ephedrine is a reflex effect of the rise in blood pressure.

Evidence that ephedrine increases the strength of contractions of the human heart was obtained by Miller (and Pendergrass) (1925) by means of fluoroscopic observations of three individuals, in every one of whom the excursion of the ventricular and aortic shadows was greater after ephedrine than before. At the same time the apex impulse became visibly and palpably more forceful and the heart sounds became louder. These observations furnish an explanation of the palpitation which is commonly complained of by patients receiving ephedrine. Miller (1925) has also called attention to the occasional appearance of systolic murmurs in patients who had normal sounds before ephedrine was given, and to the intensification of existing systolic murmurs by ephedrine. These murmurs may be heard at the apex alone, at the base alone (in either aortic or pulmonary area), or in all these areas. He suggested that they might be the result of distention of the cardiac chambers leading to the relative stenosis of aortic or pulmonary orifices, or to relative insufficiency of the mitral valve.

Electrocardiographic studies of the effects of ephedrine in man were made by Middleton and Chen (1927) in 11 patients, the drug being taken by mouth; seven showed no change, four developed ventricular or auricular extrasystoles, these being most marked in a patient with chronic myocarditis in whom systolic blood pressure fell 30 mm. following ephedrine. Pennetti (1928) studied the electrocardiograms of 8 subjects with normal cardiovascular systems upon subcutaneous injection of 50 mgm. of ephedrine. Five of these showed perfectly normal tracings after the drug was given, while in three there was some change—decrease or increase—in height of the R wave and prolongation of the S wave, and in one the T wave became diphasic.

The observations bearing upon the action of ephedrine upon the heart may be summarized as follows: there is no doubt that ephedrine, in large dosage, is depressant to the amphibian or mammalian heart, and may cause acute cardiac failure. This action is apparently exerted directly upon the muscular and neuromuscular tissues of the heart, and is independent of effects upon the cardiac nervous mechanism. The cardiac stimulant effect of smaller quantities of ephedrine is likewise well marked in the case of the mammalian and human heart, less so in the amphibian heart. This effect is fully comparable with that

of excitation of the accelerator nervous mechanism of the heart, by means of electrical stimuli or epinephrine. The effect of ephedrine differs from that of epinephrine in that it is apparently exerted not only upon the extreme peripheral parts of the accelerator system, but upon its ganglia as well.[1] In the cardiac effects of ephedrine one sees the same general differences from epinephrine that are evident in the effects upon blood pressure: ephedrine effects are less intense but much more prolonged, and upon increasing or repeating the dose of ephedrine the stimulant effect is increased little or not at all, or may be replaced by a depressant effect. The ability of ephedrine to increase the rate and force of heart beats is limited not only by an apparently small number of receptors, but also by its capacity for depressing heart muscle. Its cardiac stimulant effect cannot be made as intense as that of epinephrine by increasing the dosage and this fact, together with the deleterious effects of large doses upon heart muscle, make the intravenous or intracardiac administration of ephedrine inadvisable when stimulation is needed in an emergency.

c. The action on blood vessels. Ephedrine produces vasoconstriction. This was first demonstrated in 1917 by Amatsu and Kubota by means of perfusion experiments. They observed constriction of vessels of frogs' legs upon perfusion with a concentration of 1 in 10,000 of ephedrine hydrochloride; the vessels of the ear of the rabbit were constricted by solutions ranging from 1 in 2,000 to 1 in 20,000; constriction was also noted in the perfused vessels of the intestine, spleen, and kidney of the dog. Their results have been confirmed by perfusion experiments made by Chen and Schmidt (1924) on the dog's kidney, by Chen and Meek (1926) on the kidney, spleen, and leg of the dog, by Barlow and Sollmann (1926) and by Méhes and Kokas (1929) on the frog, by Loo and Read (1928) on the toad, the latter finding a 1 in 20,000 solution effective. Other workers, while agreeing that ephedrine is a vasoconstrictor, found it a much less powerful one than these results would indicate. Thus, Kreitmair (1927) found

[1] This has been recently denied by Tainter (1929) who found that ephedrine, applied to the stellate ganglion, caused cardiac acceleration only exceptionally, and that similar effects could be produced by application to the pleura itself. He calls attention to the acidity of ephedrine solutions as a probable factor in the result obtained by Chen and Schmidt (1924).

constriction of frog's vessels with a 1 in 10 dilution of ephedrine, but none with a 1 in 100 solution; Gradinesco (1927) found only slight constriction with a 1 in 100 solution, and Schaumann (1928) obtained only slight constriction with concentrations less than 1 in 1,000. The last-named investigator found that a very small amount of epinephrine augmented the constrictor action of ephedrine, and that repeated applications or an increase in concentration of ephedrine were less effective, ineffective, or might cause dilatation of vessels.

Plethysmographic investigations have also disclosed the ability of ephedrine to constrict blood vessels, and have furnished additional information concerning its relative effectiveness upon different parts of the vascular system. Chen and Schmidt (1924) reported that intravenous injection of ephedrine in dogs caused immediate decrease in volume of the kidney only, and this decrease was followed by increase to a level far above normal. Increase in volume as blood pressure rose was usually observed in the intestines and invariably in the leg. Chen and Meek (1926) obtained similar results; they also recorded volume of the spleen and found it usually decreased during the rise in blood pressure produced by ephedrine. Rudolf and Graham (1927) noted that the volumes of intestines and leg of the dog were slightly increased at first, but subsequently decreased, indicating delayed vasoconstriction. Gradinesco and Marcu (1927) reported increase in splenic volume; kidney volume was increased following small doses, but with large ones it was first decreased, then increased. Lim, Necheles and Ni (1927), who recorded the volume of the viviperfused stomach of the dog, obtained evidence of vasoconstriction by ephedrine, but a slight increase in volume was sometimes noted.

These results leave no doubt concerning the ability of ephedrine to constrict certain blood vessels, nor concerning its status as a vasoconstrictor that is much less powerful and uniform in its effects than epinephrine. Yet it appears that the vasoconstrictor action of ephedrine, like that of epinephrine, is essentially peripheral, and is not dependent upon stimulation of the vasomotor center or other parts of the central nervous system. This was shown by Amatsu and Kubota (1917), and by Chen and Schmidt (1924), who found ephedrine effective in raising the blood pressure of animals whose central nervous systems were destroyed or paralyzed. The same conclusion was

reached by Marcu and Gheorghiu (1927) as a result of observation of simultaneous changes in carotid and crural blood pressures, and by Heymans (1928), who employed crossed-circulation experiments to exclude the central nervous system; the former found that ephedrine still raised blood pressure after exclusion of cardiac and splanchnic effects. But since plethysmographic experiments have shown that vasoconstriction is evident only in certain organs (kidney, spleen) as blood pressure rises following ephedrine it is clear that the effect is not exerted in the same degree upon all blood vessels—a conclusion that is equally applicable to epinephrine.

Concerning the part of the vascular bed that is affected by ephedrine, little information is available. Kreitmair (1927) reported that a 1 per cent solution of ephedrine, locally applied to the web or tongue of a frog, causes constriction of arterioles and obliteration of capillaries. Chen (unpublished) studied the circulation of the frog's tongue, web, mesentery, and kidney, but was unable to detect any significant changes upon local application or intravenous injection of ephedrine until a sufficient quantity had been given to depress the heart, when the observed effects could be attributed wholly to cardiac depression. H. C. Hou (personal communication) obtained practically the same result. It appears, therefore, that ephedrine has not the intense constrictor action upon the extremely peripheral parts of the vascular bed that is so conspicuous a feature in the case of epinephrine. This may explain to a considerable degree the greater readiness with which ephedrine is absorbed into the circulation; it also makes ephedrine unsuitable for combination with local anesthetic mixtures.

The action of ephedrine upon blood vessels that are not markedly constricted by epinephrine (coronary, pulmonary, cerebral) has not been studied systematically. Chen and Schmidt (1924) found that ephedrine, like epinephrine, increased the outflow from the coronary vessels of the rabbit's heart perfused by Langendorff's method. Schmidt (1928) reported increase in venous outflow from the brains of dogs and cats given pressor doses of ephedrine, as well as epinephrine, but pituitrin had the same sort of effect. The effects upon the pulmonary circulation apparently have not been studied.

Some information has been obtained concerning the action of

ephedrine upon human blood vessels. Marcu (1926) applied a plethysmograph to one arm and a cuff for sphygmomanometry to the other. He concluded that minimal doses of ephedrine (less than 1 mgm. by vein) caused dilatation followed by constriction of abdominal vessels, while small doses (less than 10 mgm.) caused generalized constriction in splanchnic and other vessels; larger doses had the same general effect, but constriction of abdominal vessels became relatively more marked. Apparently the splanchnic circulation of man is most susceptible and is most powerfully affected by ephedrine, and this is in harmony with the results of plethysmographic experiments in animals. Rowntree and Brown (1926) studied the effects of intradermal injection of 10 per cent ephedrine in saline solution. The reaction was a small red central area surrounded by a patchy white border of irregular outline and inconstant appearance; reflex erythema was frequent. Epinephrine, similaly injected, caused a small white central area, surrounded by a zone of erythema. This confirms the results obtained by observation of the effects of ephedrine on capillaries of the frog in indicating that ephedrine has little or no constrictor effect upon capillaries. The ability of ephedrine to constrict the vessels of the nasal mucous membrane of man when the drug is taken by mouth has been proved repeatedly and will be considered in the section dealing with clinical uses.

3. The action on respiration

Apart from its effect upon the respiratory passages, which are due wholly to peripheral actions, ephedrine is a stimulant to the respiratory center, resembling caffeine in its effects. In intact animals small doses of ephedrine (5 mgm. per kilogram subcutaneously, 1 mgm. per kilogram by vein) have no significant effect upon respiratory rate or depth, and the same is true of human beings given therapeutic doses (Jansen 1926). In anesthetized animals the results appear to be somewhat variable in detail but stimulation is a common result. Fujii (1925) found that the respiration of urethanized rabbits was increased in rate and decreased in depth by ephedrine in dosage of 10 mgm. per kilogram. Kreitmair (1927), using cats anesthetized with urethane and ether, found that 5 mgm. of ephedrine per kilogram caused increase in depth of respiration, rate being unaffected.

Suzuki (1928) gave larger doses (30 mgm. per kilogram) to rabbits and noted as a rule an increase in depth with decreased rate of breathing, though occasionally rate was increased markedly. Schmidt (1929) found that ephedrine was more regularly effective than any of the conventional respiratory stimulants in combating extreme respiratory depression due to morphine. Toxic or lethal doses of ephedrine always produce acceleration of respiratory rate immediately before final failure of breathing, in intact or anesthetized animals (Miura, 1887; Chen, 1926; Kreitmair, 1927); this may be due to a large extent to acute circulatory depression.

The action of ephedrine upon the respiratory center seems to consist of two distinct components: first, an increase in blood supply of the center, due to the pressor effect; second, a direct stimulant action upon the cells of the center. The result of ephedrine action is therefore equivalent to that of a combination of epinephrine and caffeine. Ephedrine appears to be the most useful single respiratory stimulant that is available at present (Schmidt, 1929).

4. The action on smooth muscle

In the effects that have been considered up to this point ephedrine differs only quantitatively from epinephrine. When the actions of the two agents are compared upon smooth muscle in general however, it is soon evident that the effects of ephedrine are sometimes opposite to those of epinephrine. Since the latter are due, in so far as is known at present, wholly to stimulation of the sympathetic innervation of the muscle, it is clear that ephedrine either lacks this power or else applies it to the various parts of the sympathetic system with relative intensities that are different from those of epinephrine.

a. Pupil. Ephedrine produces mydriasis when applied locally to the conjunctiva or when absorbed into the circulation. This was first demonstrated by Miura (1887) and by Takahaski and Miura (1889) in dogs, cats, and rabbits, as well as humans; the pupils of chickens and pigeons were not dilated by ephedrine. These earliest workers left little to be added to the analysis of this feature in the action of ephedrine. They found that the light and accommodation reflexes were not abolished by the drug; that electrical stimulation of the oculomotor nerve caused contraction of the pupil dilated by ephedrine;

that section of the cervical sympathetic nerve or extirpation of the superior cervical ganglion did not prevent ephedrine mydriasis; that the latter could be diminished or overcome by means of muscarine, pilocarpine, or physostigmine, as well as nicotine; that atropine did not cause further mydriasis after ephedrine had produced its complete effect. They concluded (1889) that ephedrine mydriasis is due to stimulation of the sympathetic pupillo-dilator mechanism and does not involve paralysis of the parasympathetic (oculomotor) pupillo-constrictors. The results have been confirmed in all respects by Grahe (1895), by Hirose (1915) and Miura (1912) on enucleated eyes of frogs, by Chen and Schmidt (1924) on the eyes of dogs, cats, rabbits and men, by Koppányi (1928) on the eyes of guinea-pigs, and by Poos (1927) on the isolated sphincter and dilator muscles of the eyes of rabbits and calves. The latter was able to show that ephedrine—like epinephrine and cocaine—causes increase in tone of the dilator muscle, decrease in that of the sphincter; the stimulant effect upon the dilator was augmented by increasing the alkalinity of the solution. This may explain the result obtained by Munch (1928), confirmed by Swanson, Thompson and Rose (1929), that ephedrine base is a more powerful mydriatic in the cat than is the alkaloidal sulphate or hydrochloride.

Chen and Schmidt (1924) confirmed the results of Miura, adding the observation that ephedrine does not cause loosening of corneal epithelium. Kreitmair (1927) stated that while ephedrine injected intravenously is about equally effective in causing mydriasis in dogs, cats, and rabbits, local application to the conjunctiva causes much less mydriasis in cats than in the other animals.

Comparing the pupillary effects of ephedrine with those of epinephrine, an essential difference is at once evident in the fact that while epinephrine has little or no effect upon the normal pupil, whether the drug is applied locally or injected intravenously, ephedrine is a highly effective dilator of the normal pupil, by any mode of administration. Schmidt (unpublished results) recently compared the effects of the two drugs upon the pupils of three rabbits each of whom had had the left superior cervical sympathetic ganglion removed several months previously: epinephrine, locally applied to both eyes or injected intravenously, dilated only the pupil of the operated side, while ephedrine,

similarly exhibited, dilated both pupils, but the normal one more markedly than the other; pituitrin, locally applied, did not dilate either pupil. In these animals, as well as in the ones previously used by Chen and Schmidt (1924), cocaine dilated only the normal pupil. It is obvious that denervation does not sensitize the pupil to the effect of ephedrine as it has long been known to do to that of epinephrine. On the other hand, the structures upon which ephedrine acts to produce mydriasis do not degenerate after excision of the superior cervical ganglion, as appears to be the case with those upon which cocaine acts. Yet the action of all three drugs is essentially peripheral, as shown not only by the fact that the effect is limited to the eye to which they are applied, but also by the results obtained with the excised surviving muscle (Poos, 1927). The sensitization of the denervated pupil to epinephrine was attributed by Meltzer and Auer (1904) to the removal of inhibitory influences exerted by the ganglion upon the peripheral receptors with which epinephrine reacts, assuming that the latter do not degenerate under such conditions. On this basis, it would be necessary to conclude that cocaine acts upon receptors all of which degenerate following removal of the ganglion, and that ephedrine, the effects of which are weakened but not abolished by such removal, acts partly upon cocaine-like receptors and partly upon epinephrine-like ones.

b. Gastro-intestinal tract. In contrast with the effects of epinephrine, which are uniformly like those of stimulation of the sympathetic innervation of this system, the effects of ephedrine appear to be irregular and uncertain.

The effects upon the œsophagus were studied by To (1921), using the isolated organ of the frog. He found that ephedrine relaxed its tone in concentration of 1 in 2,000, and exerted a potentiating effect when given together with atropine or papaverine.

The crop muscles of the pigeon were found by Hanzlik and Butt (1928) to be thrown into contraction by ephedrine in dosage of 10 to 20 mgm. per kilogram; the effect involved both circular and longitudinal musculature, lasted 5 to 10 minutes, and was not prevented by atropine, though it was reduced by cocaine.

The effects of ephedrine upon the stomach in situ were studied in unanesthetized dogs with permanent fistulae by Kinnaman and Plant

(1927); they gave 5 mgm. of ephedrine per kilogram by vein, and found prompt and marked relaxation of gastric tone with inhibition of gastric motility, lasting 4 to 5 hours. Schmidt (unpublished) recently had the opportunity of repeating this experiment upon a single dog; following subcutaneous injection of 1 mgm. of ephedrine per kilogram, there was relaxation of tone and inhibition of gastric peristalsis for about 2 hours. In none of these experiments was there any trace of a stimulant action by ephedrine upon the gastric muscle of the unanesthetized dog, and inhibition (the epinephrine-like effect) was uniformly observed. M'Crea and Macdonald (1928) found that ephedrine, like epinephrine, inhibited gastric peristalsis and caused fall in intragastric pressure of anesthetized cats. The effects of ephedrine upon the human stomach have also been investigated. Pollak and Robitschek (1926) made roentgenologic studies: they observed an increase in gastric peristalsis, leading to expulsion of the barium meal into the duodenum, ½ to 1 minute after the subject had swallowed 20 drops of 10 per cent solution of ephedrine. They state that epinephrine caused a similar effect, which, they believe, may have been due to direct excitation of the musculature or to reflex stimulation consequent upon irritation of the mucous membrane. Marcu and Savulesco (1928) recorded gastric motility by means of a balloon which was swallowed and connected to a water manometer; upon intravenous injection of 1 cc. of a 1 in 500,000 solution (0.002 mgm.) of ephedrine they observed transitory contraction of the stomach, 0.02 to 0.05 mgm. had no effect, while 0.1 mgm. caused inhibition of contractions for about 10 minutes; upon intravenous injection of 20 mgm. of ephedrine, there was marked and prolonged inhibition of gastric movements, with a stimulant after-effect.

The effects upon the small intestine in situ have received less attention. Using unanesthetized dogs with fistulae of the ileum, Kinnaman and Plant (1927) found that ephedrine, injected intravenously, uniformly caused immediate relaxation and inhibition of motility, followed by a stimulant effect that became more marked as the dose was increased. With 0.5 to 1 mgm. per kilogram inhibition was marked, lasted 30 minutes to 2 hours, and was followed by only slight stimulation, but with 5 mgm. per kilogram the period of inhibition was shorter and the stimulant after-effect was more marked. Schmidt

(unpublished experiments) tried the effect of intramuscular injections of 2 mgm. of ephedrine per kilogram in four unanesthetized dogs with fistulae of the ileum, making 13 observations in all. In eight, there was pure decrease in motility, ranging from slight to marked; in two there was no distinct effect; in two there was brief inhibition followed by increase in motility; in only one case was there pure stimulation after ephedrine, and this was insignificant compared with the effect of local application of an aromatic water or intramuscular injection of 5 mgm. of morphine.

The large intestine in situ showed only depression of tone and motility in every one of the few observations made. Kinnaman and Plant (1927) found this to be the case in unanesthetized dogs with colonic fistulae, and Schmidt (unpublished), using two such dogs, saw distinct decrease in tone and prolonged inhibition of motility following intramuscular injection of 2 mgm. of ephedrine per kilogram, if active movements were present before the drug was given; if not there was no effect. As far as we know there has never been any sign of a stimulant effect by ephedrine upon the large intestine in situ.

The results of experiments upon the gastro-intestinal tract in situ therefore indicate that the effects of ephedrine are, on the whole, very similar to those of epinephrine. With isolated strips of intestinal muscle, surviving in a warm saline solution, the results are much less uniform, some workers finding that ephedrine is only depressant, others reporting depression and stimulation, still others observing only stimulation. Thus, Amatsu and Kubota (1917) found ephedrine to be essentially depressant to isolated intestine of cats and rabbits, and the same result was obtained by To (1921), by Fujii (1925), and by Chen and Schmidt (1924) in rabbits. The last-named investigators found that the inhibitory effect of ephedrine could be readily overcome by means of pilocarpine or barium, and was not prevented by nicotine, thus showing that the effect was not due to depression of parasympathetic nerve endings, muscle fibers, or intrinsic ganglia (plexus of Auerbach). Subsequent workers have failed to confirm these results. Nagel (1925) found ephedrine to be purely stimulant to the isolated intestine of the rabbit and cat; the inhibitory effect of epinephrine could be overcome by ephedrine. Kreitmair (1927) found the isolated intestine of the cat to be relaxed by low concen-

trations (1:1,000,000 to 1:100,000) of ephedrine, but slightly stimulated by a stronger one (1:6,000); the latter effect could be prevented completely by atropine. Reinitz (1928) reported that isolated rabbit intestine was sometimes inhibited, often stimulated, sometimes inhibited and then stimulated, by the same concentration of ephedrine; he stated that atropine had no significant influence upon the stimulant response. Méhes and Kokas (1929) reported stimulation of isolated rabbit intestine by weak concentrations (1:150,000 to 1:50,000) of ephedrine, relaxation with a stronger one (1:10,000). Rudolf and Graham (1927) found only slight and transitory depressant effects by ephedrine upon isolated rabbit intestine. Lim and Chen (1928) noted only stimulation of cat intestine, isolated but with intact circulation, upon the addition of ephedrine. De Eds, Rosenthal, and Voegtlin (1928) reported pure stimulation of rabbit intestine exposed to a 1:5,000 solution of ephedrine, and Halsey (1928) found no instance, among many preparations of isolated rabbit intestine, of anything but stimulation by ephedrine.

Isolated large intestines of the rabbit were found by Kreitmair (1927) to be affected like the small by ephedrine, i.e., they were depressed by weak solutions, stimulated by strong ones and the latter effect could be prevented by atropine. Thienes (1929) reported that epinephrine depression of isolated large intestines of cats, rabbits, dogs, rats and guinea-pigs was antagonized by ephedrine.

It may safely be assumed that any of these preparations would have been inhibited by epinephrine, so that it is very evident that the effects of ephedrine upon isolated muscle of the gastro-intestinal tract are inconstant. A probable explanation for this will be presented later (page 52). It should be pointed out here that the effects of ephedrine upon movements of the gastro-intestinal tract in situ appear to be much more nearly like those of epinephrine than is the case when the two agents are tested upon isolated muscle preparations. The reason for this is unknown: it is possible that central nervous influences or indirect actions through the suprarenal glands (see page 55) play a part in these effects of ephedrine in the living animal. Whatever the explanation, the effects upon the gastro-intestinal tract in situ are those which are of therapeutic importance, and there is no evidence at present that ephedrine can properly be employed as a stimulant to gastro-intestinal motility.

c. Uterus. All of the data available at present were obtained with isolated tissue excepting a few experiments of Chen and Schmidt (1924), who found that the dog's uterus in situ was stimulated by ephedrine. To (1921) reported that the isolated uterus of the rabbit or rat was depressed by dilute solutions of ephedrine (1:20,000 and 1:100,000 to 1:10,000 respectively), while stronger solutions (1:10,000 and 1:3,300 to 1:2,000 respectively) caused stimulation. Chen and Schmidt (1924) found that the isolated rabbit uterus was uniformly stimulated by ephedrine, with only one exception—the uterus of a recently delivered rabbit. Stimulation was the only effect of ephedrine upon isolated uterus in the experiments of Fujii (1925) on rabbits, of Nagel (1925) on guinea pigs, of Kreitmair (1927) on rabbits, of De Eds and Butt (1927) and De Eds, Rosenthal, and Voegtlin (1927) on rabbits and guinea-pigs, of Thienes (1929) on cats, rabbits, dogs, rats and guinea-pigs, of Reinitz (1928) on rabbits, and of Curtis (1929) on guinea-pigs and cats. The uterus of the albino rat, however, is uniformly relaxed by ephedrine (Liljestrand, 1927).

These results are quite unlike those obtained with epinephrine, which usually relaxes the isolated non-pregnant uterus of the cat and frequently relaxes the non-pregnant guinea-pig uterus. In fact Thienes (1929) found that ephedrine prevented the inhibitory effect of epinephrine upon various uteri. Reinitz (1928) reported that very small quantities of ephedrine augment the (stimulant) effect of epinephrine upon the isolated rabbit uterus, but larger quantities reduce it.

In general, the action of ephedrine upon the isolated uterus is characteristically a stimulant one, and bears no constant relation to the action of epinephrine. Whether the same is true of the effects upon the intact uterus in situ has not been determined, for no experiments have as yet been made with animals whose uteri are relaxed by epinephrine.

d. Urinary tract. Hofbauer (1928) tested the effect of ephedrine upon the isolated ureter of the pig: he found that the rate of contractions of both circular and longitudinal muscle was increased by ephedrine, and that it was occasionally possible, by means of ephedrine, to restore contractions after they had been arrested by sodium glycocholate; the effects of epinephrine were qualitatively the same but it was a much more powerful stimulant than ephedrine. His results have been confirmed by Roth on the dog's ureter.

Macht (1929) studied the effects of ephedrine upon the trigonal and fundus portions of the urinary bladders of rabbits, cats and rats. It has been shown repeatedly that epinephrine causes contraction of the trigone and relaxation of the fundus. Ephedrine caused contraction of both portions. Liljestrand (1927) obtained the same results with the rabbit's bladder.

e. Bronchi. One of the most useful therapeutic actions of ephedrine is its ability to relieve or to prevent the paroxysms of asthma. Animal experimentation has shown from the start that ephedrine, like epinephrine, is able to relax bronchial spasm induced by various poisons. Amatsu and Kubota (1917) were the first to demonstrate this effect in rabbits whose bronchi had been thrown into spasmodic contraction by means of pilocarpine, muscarine, or peptone. They also found that isolated bronchial muscle of the cow was relaxed by ephedrine, even in such low concentration as 1 in 80,000. These results led them to recommend ephedrine in the treatment of asthma. Chen and Schmidt (1924) observed relaxation of the bronchial spasm produced by physostigmine in a dog, and stated that the effect of ephedrine was weaker than that of epinephrine. Kreitmair (1927), Villaret, Justin-Besançon, and Vexenat (1929), and Swanson (1929) have confirmed these results by various methods, but Halsey (1928) reported only exceptional bronchodilatation by ephedrine. It is generally agreed that ephedrine may fail to relax bronchial spasm when epinephrine is effective. It is generally assumed that the bronchodilator action of ephedrine is analogous to that of epinephrine and is due to stimulation of sympathetic nerves, which are inhibitory to this muscle; this has not, however, been definitely proved to be true. The effect is largely if not wholly peripheral, for it is elicited in excised tissue and in pithed animals.

5. Action on secretions

a. Saliva. Grahe in 1895 studied the action of ephedrine and pseudoephedrine on the submaxillary flow in a dog and found that the first intravenous injection has no effect while repeated injections gradually diminish the flow. Chen and Schmidt, and Chen investigated the same question in a series of dogs. In anesthetized animals, ephedrine in a dosage of 1 to 2 mgm. per kilogram produces inconsistent

results. Occasionally it increases the submaxillary flow, and this occurs in spite of atropinization, but in the majority of cases it has no effect. Larger doses (25 mgm. per kilogram or more) in non-anesthetized dogs may cause profuse salivation. When a dose slightly below the M.L.D. is administered, the increase in salivary flow is a constant feature.

b. Gastric secretion. Chen in Lim's laboratory studied the action of ephedrine on the gastric secretion in dogs with Pavlov or Heidenhain pouches. Ephedrine injected subcutaneously unmistakably increases the gastric secretion both in volume and in acidity, although to only a small extent. There is no difference between the Heidenhain and Pavlov preparations.

c. Pancreatic secretion. In anesthetized dogs with a cannula in the pancreatic duct ephedrine, given intravenously, does not change the pancreatic secretion, as shown by Chen. In non-anesthetized dogs with a pancreatic fistula, subcutaneous injections of ephedrine also gave negative results. Fonseca and Trincao (1928) reported that ephedrine caused decrease in pancreatic secretion.

d. Intestinal secretion. Dogs with Thiry-Vella fistula do not show any response in their intestinal secretions to the subcutaneous injection of ephedrine, as reported by Chen.

e. Bile. In acute experiments with anesthetized dogs, there is no demonstrable alteration of bile flow after ephedrine injected intravenously (Chen). The same can be said for non-anesthetized animals with a pancreatic biliary fistula when ephedrine is injected subcutaneously. Kreitmair, using larger doses (50 to 100 mgm. per dog), found an increase of bile flow from the biliary fistula, with a reduction of the dry matter. The increase in volume continues for more than three days.

f. Sweat. Chen and Schmidt determined the sweat secretion of an anesthetized cat and could not detect any increase after ephedrine was injected into the paw. Kreitmair arrived at the same conclusion.

In men a therapeutic dose of ephedrine occasionally produces diaphoresis. It is interesting to note that perspiration caused by the use of Ma Huang, firmly believed in by the Chinese and described by Li Shih-Cheng in his Pentsao Kang Mu, although not experimentally proved in animals, has been clinically confirmed in many reports.

g. Lymph. With the coöperation of M. Kayumi, Chen and Schmidt studied the influence of ephedrine on lymph flow, collected from the thoracic duct of anesthetized dogs. It regularly causes an increase in lymph, which reaches its maximum about 15 minutes after the intravenous injection.

h. Urine. In anesthetized dogs the urine flow appears to follow the plethysmograph of the kidney volume, as observed by Chen and Schmidt. There is suppression during the primary vasoconstriction, but an increase during the secondary dilatation. After repeated doses the urine is invariably suppressed. Intact rabbits which receive daily intravenous injections of ephedrine show a well marked diuresis. Starr, coöperating with T. G. Miller, studied the output of urine in a series of 16 men, in correlation with the systolic blood pressure. He divided his results into three groups: (1) those showing a rise of blood pressure without diuresis and with albuminuria; (2) those showing no rise in pressure with no diminution of urine and no albuminuria; and (3) those showing a rise of pressure with diuresis and albuminuria. The occurrence of albumin in the urine is transitory, for it disappears when the effect of the ephedrine wears off. In those that show an increase in pressure but no diuresis, the albuminuria is due to renal vasoconstriction, while in those that show rise in pressure and increase in urinary output, it is probably due to the alternate constriction and dilatation of the glomerular functional units. Kreitmair observed diuresis on himself after the ingestion of 50 mgm. of ephedrine, lasting for 2 to 3 hours. Gradinescu and Marcu also call attention to the fact that the variation in urine flow depends on vascular changes.

6. Action on the blood

a. Blood cells. Hess reported leucocytosis after ephedrine, reaching its maximum at the same time as the blood pressure attains its highest level. Marcu and Petresco studied the blood changes in men on intravenous injection of ephedrine. A dose of 20 mgm. increases the leucocytes within the first five minutes, lasting for more than one hour and 40 minutes. The leucocytosis consists chiefly of lymphocytosis. The red blood corpuscles are also increased, with a corresponding increase in hemoglobin. The maximum is attained in about 40 minutes. Ephedrine in a dosage of 60 mgm., given intravenously, pro-

duces a leucocytosis and erythrocytosis which lasts for two hours or longer. These changes, the authors believe, indicate a concentration of the blood. Pathological conditions apparently modify this reaction. Thus, Marcu and Petresco observed with a dose of 20 mgm. intravenously a decrease of red blood corpuscles and leucopenia in a case of Addison's disease, and leucopenia but erythrocytosis in a case of Hodgkin's disease. Binet, Arnaudet, Fournier and Kaplan observed an increase in platelets in addition to erythrocytosis and leucocytosis in chloralosed dogs. The maximal increase in the platelets is reached at the end of 5 to 15 minutes after the intravenous injection of 3 mgm. of ephedrine per kilogram. According to these investigators the increase in the formed elements of the blood is due to contraction of the spleen, for splenectomy prevents this reaction and previous administration of yohimbine, which paralyzes the contractors of the spleen, abolishes such a response.

b. Blood chemistry. Chen and Schmidt studied the effect of ephedrine on the blood sugar in two anesthetized dogs. Their results were inconclusive. Negative or doubtful results were obtained by T. G. Miller in men, by Hess in men, by Kreitmair in rabbits, by Rudolf and Graham in diabetics, by Tu in men, and by Haintz in men. Hyperglycemia may be produced in animals by doses larger than the pressor ones. Thus, Nagel determined the hyperglycemic dose in rabbits to be 25 mgm. per kilogram, injected intravenously. Wilson found it to be 10 to 15 mgm. per kilogram (intravenously or subcutaneously) in dogs, and 20 to 30 mgm. per kilogram (intravenously) in rabbits. According to Nitzescu, hyperglycemia occurs in dogs when they are in full digestion but is absent when they are previously starved. The doses he used were 0.5 to 3.0 mgm. per kilogram, given intravenously. The simultaneous administration of glucose and ephedrine does not increase the hyperglycemia produced by glucose alone but lengthens its duration. A limited increase in blood sugar in men with therapeutic doses (5 to 100 mgm.) of ephedrine given orally was observed by Pollak and Rabitschek and by Lublin. Radoslav and Stoïcesco administered ephedrine to men by intravenous injection. Doses of 5 to 90 mgm. produce a diphasic reaction—a primary hyperglycemia followed by hypoglycemia. The blood sugar returns to normal in about two hours.

After the intravenous injection of 20 mgm. of ephedrine, the serum albumin increases to the extent of 10 parts per thousand and returns to normal in 20 minutes, while the globulins are increased for two hours, as determined by Marcu and Petresco. The concentration of albumins and globulins occurred in both healthy individuals and in a case of Addison's disease and another of Hodgkin's disease. Unlike epinephrine, ephedrine does not raise the peptidase titer of the rabbit's serum (Pfeiffer and Standenath).

7. *Action on metabolism*

a. Metabolic rate. T. G. Miller reported an increase in metabolic rate in 4 cases with 100 to 125 mgm. of ephedrine injected subcutaneously. Rowntree and Brown also studied the calorigenic effects of ephedrine, given by mouth, in several diseased conditions. In 3 cases of Addison's disease there was an increase in metabolic rate in two but a decrease in the third. In a case of questionable Addison's disease and 4 cases of hypotension, an increase was also demonstrated. The effects seem to be transitory and an hour afterwards there may be a tendency to a fall of metabolic rate. A patient with endocrine obesity showed a decrease of 11 points with 50 mgm., but with 100 mgm. there was an increase of 13 points in 3 hours. In a case of pituitary tumor there was a demonstrable increase of the basal metabolic rate after 50 mgm. of ephedrine had been given. In rabbits, Dulière observed only inconsistent changes in metabolism after the administration of ephedrine.

b. Gaseous exchange. Schmidt (1928) demonstrated that ephedrine increases both cerebral O_2 consumption and CO_2 liberation. Wilson, Pilcher and Harrison, and Halsey, Reynolds and Blackberg also observed an increase in O_2 consumption with a tendency of the alveolar CO_2 to fall. After giving fructose or glucose, the R.Q. is always greater than 1, but if ephedrine and fructose are given at the same time the R.Q. becomes less than 1. According to Lublin, this means the inhibition of fat formation by ephedrine. In rabbits, Dulière constantly observed a decrease of R.Q. following the intravenous injection of ephedrine.

c. Body temperature. With toxic doses Miura in 1887 reported an elevation of temperature in dogs, rabbits and mice. Like epinephrine

and β-tetrahydronaphthylamine, ephedrine, according to Hashimoto (1915), slightly raises the body temperature (0.5° to 0.7°C.) in normal rabbits and it produces fever in those animals whose heat centers have been punctured. The dose for the production of this response is 20 mgm. per kilogram. Notwithstanding, Suzuki recently reported a slight fall in rectal temperature in rabbits, either normal, adrenalectomized or with the splanchnic nerves sectioned, using a dose of 30 mgm. per kilogram, given intravenously.

8. Action on the central nervous system

Ephedrine appears to stimulate the central nervous system. Airila in 1913 showed that chloralized rabbits can be awakened temporarily by an intravenous injection of ephedrine (10 to 20 mgm.). Morita in 1915 obtained similar results in rabbits whose cerebral hemispheres had been removed, and believes that the stimulation is subcortical. In the squid, *Loligo pealii*, doses of 5 mgm. or more make it turn blood-red within half an hour, the color persisting for twelve to twenty hours or more, as observed by Nadler. Oral administration and injection into the circulation via the heart likewise produce this dark coloration. The author attributes this change to stimulation of the central nervous system. In men moderate doses of ephedrine sometimes cause tremor, nausea, and insomnia, which in all probability is due to stimulation of the central nervous system. C. F. Schmidt obtained evidence that ephedrine directly stimulates the respiratory center. In anesthetized dogs, Johnson and Luckhardt found that ephedrine in large doses, injected intravenously or subcutaneously, causes a marked increase in the reflex excitability of the spinal cord, as measured by the knee jerk. The action is not dependent on any influence of the higher centers on the cord nor due to the hemodynamic action of the drug, since the increase in excitability of the cord outlasts the rise of blood pressure.

9. Action on the peripheral nerves and voluntary muscles

The action of ephedrine on the motor nerves has been studied by Read and Lin. They conclude that ephedrine potentiates the action of novocaine on the frog's sciatic nerve. By the addition of 0.005 per cent of ephedrine to a 1 per cent solution of novocaine the time required for blocking of the motor impulse is lessened by 80 per cent.

Ogata (1920) states that ephedrine has no local anesthetic action, meaning that it is devoid of action on the sensory nerve endings. Read and Lin, on the other hand, claim that a mixture of ephedrine with epinephrine and potassium sulphate can produce, by the wheal method, local anesthesia equal in intensity to that produced by a mixture of similar proportions and strengths of novocaine, epinephrine and potassium sulphate.

Amatsu and Kubota (1917) studied the effect of ephedrine on the frog's gastrocnemius muscle. They found that a 0.1 per cent solution raises the threshold of stimulation (electric) and produces irregular contractions on repeated stimulation with a current of constant strength, instead of a gradual fatigue curve.

10. Mode of action

In a previous review of this subject, Chen and Schmidt (1926) divided the actions of ephedrine into three categories: the therapeutically useful ones, which are due to peripheral sympathomimetic effects; the stimulant action upon the central nervous system; and the depressant action upon heart muscle. The second and third types of action were said to be exerted as a rule only by excessive dosage and were regarded as undesirable or dangerous. Subsequent developments have necessitated a modification in this characterization in so far as the central nervous effects are concerned, for it is now certain that they may be elicited by therapeutic doses in some individuals at least, and may be useful in combating the action of narcotic poisons, particularly upon the respiratory center. The action of ephedrine upon the brain cells has not been analyzed, but it appears to be comparable with that of caffeine (Schmidt, 1928). The depressant action upon heart muscle is essentially similar to that of any other myocardial depressant, and the only practical importance of this type of effect is that it imposes limitations upon the therapeutic usefulness of the drug. There is no disagreement among various workers with respect to the central nervous and myocardial depressant effects of ephedrine.

The peripheral actions of ephedrine, which are of greatest interest to the clinician, are not so simply disposed of. The earliest workers in this field (Amatsu and Kubota, 1917; To, 1921; Chen and Schmidt, 1924) were impressed with the obvious similarity of the effects of

ephedrine to those of epinephrine, and concluded that ephedrine is a sympathomimetic substance. These effects include mydriasis with preservation of light and accommodation reflexes, broncho-dilatation, cardiac acceleration and augmentation, vasoconstriction, inhibition of gastro-intestinal motility (in many cases), hyperglycemia, and occasional secretion of saliva by the atropinized submaxillary gland. In fact no other explanation is possible for these effects, taken as a whole. The question is not whether ephedrine produces sympathomimetic effects but whether its important effects are due wholly or even largely to such actions. During recent years considerable evidence having been obtained, by a number of investigators, that the peripheral effects of ephedrine differ qualitatively in some respects from those of epinephrine, the conclusion has been drawn that ephedrine owes some of its effects to direct excitation of smooth muscle, irrespective of sympathetic innervation. Those who have concluded that ephedrine acts at least partly upon muscle fibers include Nagel (1925), De Eds (1927), De Eds and Butt (1927), Pak and Read (1928), Méhes and Kokas (1929), and Halsey (1928). The question has more than theoretical importance, for if this conclusion is fully justified ephedrine should be looked upon as a drug with the clinical usefulness of pituitrin rather than that of epinephrine.

Decisive evidence upon a point of such fundamental importance as this might well be sought in investigations of the action of the drug upon simple organisms or preparations. The only pertinent investigation of the action of ephedrine upon a lower form of life is that of Nadler (1927), which has already been discussed (page 16). He concluded that ephedrine is essentially sympathomimetic, not musculotropic. However, the organism used by him is relatively complex, and the exact mechanism of the responses studied has not been established. The results seem to the reviewers to be suggestive but not conclusive evidence upon the point at issue.

A relatively uncomplicated preparation of mammalian tissue is the plexus-free strip of small intestine of the cat (Gasser: Journ. Pharmacol. Exper. Therap., 1926, xxvii, 395). This apparently has not been used to test the musculotropic power of ephedrine. One of the reviewers (S.) recently tested 12 such preparations with ephedrine. In no case was there any trace of stimulation, and depression was more

commonly observed with ephedrine than with epinephrine. The number of observations was small, but all the preparations were active, and it is reasonable to suppose that a conspicuous musculotropic action would have been disclosed if present. These results lend no support to the conception that ephedrine is musculotropic. In fact they suggest rather that the direct action of ephedrine upon smooth muscle is a depressant one, since ephedrine was more uniformly inhibitory than epinephrine.

Another suitable test-object would be blood vessels which are not conspicuously affected by epinephrine, such as those of the coronary, cerebral, and pulmonary areas. The only available information concerning the action of ephedrine upon such structures is the statement of Chen and Schmidt (1924) that coronary outflow from the perfused mammalian heart was augmented, never decreased, by ephedrine. This is far from conclusive evidence upon the point at issue, since rate and force of cardiac contractions were also increased. However, pituitrin regularly causes very marked reduction in coronary flow in such preparations. If the latter is regarded as a representative example of the effect of musculotropic agents, the result with ephedrine indicates that the latter is not musculotropic. Further information concerning the actions of ephedrine upon coronary, cerebral, and pulmonary vessels is highly desirable.

The contention that ephedrine is capable of exerting stimulant effects upon smooth muscle fibers irrespective of their innervation is based upon observations of two general sorts. These are, the influence of certain other substances (ergotoxine, yohimbine, cocaine, insulin) upon the circulatory effects of ephedrine, and the action of ephedrine upon various preparations of isolated smooth muscle. None of the evidence so far obtained by these procedures appears to be decisive.

a. Circulatory responses. The fact that ergotoxine (ergotamine) leads to a reversal of the blood pressure effect of epinephrine has led to the employment of ergotoxine as a means of discriminating between sympathomimetic and musculotropic effects on the part of other drugs which raise blood pressure. Other things being equal, a given quantity of the agent being tested should cause a fall in pressure after ergotoxine if it is sympathomimetic, while if its effects are unaltered by ergotoxine it must be musculotropic.

Among those who have tested the influence of ergotoxine upon the pressor response to ephedrine are Nagel (1925), Kreitmair (1927), De Eds and Butt (1927), Chen (1928), and Curtis (1929). All found that the pressor effect of ephedrine was reduced by ergotoxine, but Curtis was the only one who reported complete absence of such effect or an actual reversal after ergotoxine, though a reversal of epinephrine effects was clearly demonstrated in every case. Curtis attributed his success to the use of smaller quantities of ephedrine and larger doses of ergotoxine than had been used by his predecessors. Until this is confirmed, however, it appears proper to conclude that while ergotoxine may diminish or even prevent the pressor effect of ephedrine, an actual reversal, similar to that of epinephrine, is not the characteristic result.

These results have been interpreted as strong evidence in favor of a musculotropic action by ephedrine, but such conclusion is by no means obligatory, for two reasons: First, as has been emphasized repeatedly (Chen and Schmidt 1924, 1926; Chen and Meek, 1926; Chen, 1928; Curtis, 1928), the pressor effect of ephedrine is due more to increased cardiac action than to vasoconstriction, while in the case of epinephrine the reverse is true. It is well known that ergotoxine, in quantity sufficient to paralyze vasoconstrictor receptors and therefore to produce the epinephrine reversal, has much less effect upon the cardiac accelerator system (see Chen, 1928). It is through the latter system that ephedrine exerts much of its influence upon blood pressure. Consequently one need not expect the pressor effect of ephedrine to be abolished by ergotoxine until the latter is present in sufficient quantity to paralyze the cardiac accelerator system, and Curtis (1928) states that with sufficiently large doses of ergotoxine the pressor effect of ephedrine can be completely prevented. These objections to the conclusions derived from the ergotoxine experiments have been raised by Chen (1928) and by Curtis (1928).

Second, it must be remembered that the epinephrine reversal by means of ergotoxine presupposes a powerful stimulant action by epinephrine upon vasodilator nerves, but there is no reason to believe that ephedrine possesses such an action. For, as has already been pointed out (page 20), the smallest effective doses of ephedrine produce only a rise in blood pressure, and as the effects of ephedrine wear

away blood pressure returns to normal, not to a subnormal level. One of the outstanding advantages of ephedrine over epinephrine as a constrictor of nasal blood vessels is the absence of after-dilatation in the case of ephedrine. There is no decisive evidence upon this point, but these observations suggest strongly that the effects of ephedrine upon blood vessels are dominantly if not exclusively motor (constrictor), while in the case of epinephrine inhibitory (dilator) actions are conspicuous (Dale, 1906). The present situation is therefore practically identical with that encountered by Barger and Dale (1910) in their investigation of sympathomimetic bases. They found that ergotoxine reduced but did not reverse the pressor effect of amino-aceto-catechol or *dl*-amino-ethanol-catechol, while it led to complete reversal of the effects of methylamino-catechol or *dl*-epinephrine. The difference was attributed to a greater predominance of inhibitory (vasodilator) actions on the part of the latter substances, though the effects of all were regarded as purely sympathomimetic. The failure of ephedrine to produce a fall in blood pressure after ergotoxine cannot therefore be regarded as proof that ephedrine is not sympathomimetic.

The above considerations probably apply also to the effects of yohimbine, which Raymond-Hamet (1927) found to exert an influence like that of ergotoxine: the pressor response to epinephrine was inverted, while that to ephedrine was only reduced.

Cocaine is another agent which has been used to determine whether a pressor drug is sympathomimetic or musculotropic, as a result of the work of Tainter and Chang (1927). They found that a small dose of cocaine augmented the pressor effect of epinephrine, but reduced or abolished that of tyramine, the latter being regarded as musculotropic. De Eds (1927) and Pak and Read (1928) found that cocaine also reduced the pressor effect of ephedrine. Chen (1928) was unable to confirm this conclusion; he believed that the result was due simply to the fact that a second dose of ephedrine is less effective than the first even if no cocaine is given between them. However, Tainter (1929) has recently shown that cocaine, in dosage which augments the pressor effect of epinephrine, may reduce or abolish that of ephedrine.

These results have been interpreted as evidence that ephedrine is not sympathomimetic, but musculotropic, in its circulatory effects.

Yet, as far as the reviewers are aware, no evidence has been presented that cocaine augments the effectiveness of sympathetic nerve excitation by anything but epinephrine, and this particular effect might well be a drug synergism, peculiar to epinephrine, with no relation to sympathetic stimulation *per se*. Nor is there any evidence that reduction of pressor effectiveness by cocaine is an index of musculotropic action. In fact Tainter has recently reported (XIII International Physiological Congress) that cocaine neither increases nor decreases the effectiveness of barium and pituitrin. If one grants the validity of the assumption that any agent, to be sympathomimetic, must duplicate all of the peculiar effects of epinephrine, the cocaine test, like the ergotoxine one, indicates that ephedrine is neither sympathomimetic nor musculotropic.

Another agent which modifies the circulatory response to epinephrine much more than that to ephedrine is insulin. Csépai and Pinter-Kováts (1927) found that insulin prevents the pressor effect of epinephrine, but not that of ephedrine. The significance of this observation, apart from an indication that the circulatory effects of ephedrine are in some way different from those of epinephrine, is unknown to the reviewers.

It seems to the reviewers that these various circulatory responses, in the present state of our knowledge, can show only whether a substance does or does not elicit certain effects that are characteristic of epinephrine. If they are to be used for the purpose of determining whether a new drug is or is not likely to be of practical value as a substitute for epinephrine, one must consider the fact that ephedrine, which, according to all these tests, is not epinephrine-like, has amply proved its practical value as a substitute for epinephrine. The reviewers do not believe, therefore, that absence of epinephrine-like responses in the ergotized or cocainized animal can be regarded as convincing evidence of lack of sympathomimetic action on the part of other substances.

b. Effects upon smooth muscle. In considering the work that has been done upon this subject (pages 33–40) it was pointed out that the effects of ephedrine upon uterus and bladder fundus appear to be uniformly stimulant, though epinephrine may be depressant; that the surviving small intestine may be stimulated or depressed by ephe-

drine though invariably depressed by epinephrine. Apparently the only smooth muscles that are uniformly relaxed in vitro by ephedrine are found in the bronchi, the sphincter pupillae and the uterus of the albino rat. While it is somewhat difficult to see why a substance which acts directly upon smooth muscle fibers should stimulate some and depress others, it is equally difficult to see why a substance which owes its effects to sympathomimetic actions should so frequently lead to contraction of structures that are relaxed by epinephrine.

Considering first the isolated small intestine, however, a reason for this discrepancy is readily found in an action by ephedrine upon motor ganglia as well as inhibitory endings. Chen and Schmidt (1924, fig. 5) showed a tracing which illustrated the epinephrine-like effect of ephedrine after the ganglia had been paralyzed with nicotine. This procedure has recently been repeated by one of the reviewers (S.) with preparations made from the small intestines of cats, dogs, and rabbits, and the results have been uniformly like the earlier ones. In no instance did ephedrine fail to exert a typical sympathomimetic effect after nicotine, while stimulation of strips from adjacent parts of the bowel was frequently observed when ephedrine was applied before nicotine. Reference has also been made (page 47) to the uniform absence of stimulant effect by ephedrine upon plexus-free preparations of small intestine. It appears, therefore, that the intestinal effects of ephedrine consist in a combined stimulation of ganglia (plexus of Auerbach), which causes increased motility, and of inhibitory sympathetic endings. When the ganglionic action is excluded by means of nicotine or removal of the plexus, the sympathomimetic action is clearly and uniformly manifested.

In the case of the uterus, the corresponding information is not available. Ephedrine is almost invariably stimulant to isolated uteri, whether epinephrine is stimulant or inhibitory, and this argues in favor of the musculotropic or pituitrin type of effect. Ergotoxine has been added to the solution in which the uterus was immersed, by Nagel (1925), Kreitmair (1927), De Eds and Butt (1927), Reinitz (1928), and Curtis (1929). This substance should paralyze motor sympathetic nerve endings, and uteri so treated were uniformly inhibited by epinephrine, but all observers except Curtis reported that ergotoxine did not prevent the stimulant action of ephedrine: he

stated that by means of large doses of ergotoxine the effects of ephedrine could be prevented though never reversed. It may be, therefore, that the effects of ephedrine upon the isolated uterus are indeed sympathomimetic, but are exerted mainly if not exclusively upon motor parts of the system, the inhibitory parts being affected much less or not at all—an analogy to the effects upon blood vessels.

The stimulant action of ephedrine upon the intestine being apparently similar to that of nicotine (i.e., ganglionic), a similar action upon the uterus may be regarded as a possibility. This has not been investigated. It is not possible at present to make a plexus-free preparation of uterine muscle. The effects of nicotine upon the uterus (virgin organ of the cat) were found by Barger and Dale (1910) to be inhibitory in vivo but stimulant in vitro. In current terminology, this would imply that nicotine is sympathomimetic in vivo, musculotropic in vitro. Barger and Dale, however, believed that the inhibitory effect in vivo was due to stimulation of sympathetic ganglia which rapidly lose their sensitivity when the uterus is excised. They did not explain the stimulant action in vitro, but it can scarcely be called musculotropic because nicotine does not stimulate ganglion-free smooth muscle of the intestine (Gasser, 1926).

The situation appears to be rather obscure, and the reviewers believe that the true explanation of the uterine effects of ephedrine can be given only when more is known about the intrinsic innervation of the organ.

The situation with respect to the urinary bladder muscle is much the same. The only data are those of Macht (1929) and Liljestrand (1927) (see page 40, above). These effects of ephedrine are like those of pituitrin, unlike those of epinephrine. The results are equivocal evidence for or against a musculotropic action by a drug that appears to affect certain ganglia as well as endings, and to stimulate motor sympathetic nerves more powerfully than inhibitory ones.

It has been claimed by Fujii (1925), Kreitmair (1927), Reinitz (1928), and Marcu and Savulesco (1928) that ephedrine stimulates both parasympathetic and sympathetic nervous systems, but the evidence presented in support of this contention is inconclusive. Fujii (1925) believed that the constrictor action of ephedrine upon perfused blood vessels of the frog was exerted through parasympathetic

nerve structures, since it was absent when atropine was added to the perfusion fluid; however, it is well known that atropine has a vasodilator action of its own in such circumstances (Cushny, Textbook of Pharmacology, 1928, p. 347). Fujii, as well as Reinitz (1928), found that atropine prevented the stimulant action of ephedrine upon the isolated uterus, but this has not been the case in the experience of the reviewers. Kreitmair (1927) reported that the stimulant action of ephedrine upon isolated intestine was prevented or abolished by atropine, but this is denied by Reinitz (1928). Méhes and Kokas (1929) claim that atropine partly prevents the depressant action of ephedrine upon the perfused frog's heart, but this is opposed to the results of Fujii (1925) and Kreitmair (1927).

Apparently there is no better agreement concerning the preferential action of ephedrine, assuming that it acts upon both nervous systems. Kreitmair (1927) believed that minimal doses affected only the sympathetic, and that the parasympathetic was influenced only by relatively high concentrations. Marcu and Savulesco (1928), however, claim that minimal quantities stimulate the parasympathetic preferentially, while with large doses sympathetic stimulation dominates the picture, the effects of intermediate dosages being antagonistic and therefore inconstant or absent.

Further work is needed before this point can finally be settled. The conflicting opinions indicate that ephedrine certainly has no conspicuous pilocarpine-like effects, and Reinitz (1928) claimed that it actually has an atropine-like effect upon the intestine. There is no reason therefore for employing ephedrine as a parasympathetic stimulant.

As to the exact site of ephedrine actions, there is little information. Chen and Schmidt (1924) pointed out that ephedrine was able to dilate the pupil whose sympathetic (pupillo-dilator) innervation had degenerated following extirpation of the ganglion, while cocaine was ineffective. They concluded that the point of action of ephedrine was apparently peripheral to that of cocaine, the absence of effect from the latter indicating degeneration of the structures upon which it acted. Marcu and Gheorghiu (1927) have recently shown that ephedrine is able to increase the rate of a heart whose accelerator nerves have degenerated following removal of the ganglia: this also points to an

action upon structures peripheral to the finest nerve fibrils, which degenerate when the ganglion is removed. On the other hand, there is no good reason to attribute any of the peripheral effects of ephedrine to direct action upon effector substance (muscle fibers, gland cells). This makes the situation comparable to that encountered with epinephrine, and leads to the conclusion that ephedrine likewise acts upon hypothetical myoneural junctions.

However, there is reason to believe that the myoneural junctions affected by ephedrine are not the same as those affected by epinephrine, in the pupillo-dilator system at least. Reference has already been made (page 34) to a few observations which indicate that denervation does not sensitize the pupil to ephedrine, but diminishes its effectiveness. Should this be confirmed, it would suggest that some of the ephedrine receptors degenerate after denervation, as all of those for cocaine appear to do. This would imply that the point of action of ephedrine upon the pupil is at least partly central to that of epinephrine, and partly peripheral to that of cocaine.

It has been suggested by several workers that many of the peculiarities in the action of ephedrine could be explained on the basis of an increased secretion of epinephrine by the suprarenal glands as a result of absorption of ephedrine. This would account for the effects of ephedrine upon metabolism, blood sugar, etc. and for epinephrine-like effects upon small intestines in situ, not in vitro. The question has a practical significance in connection with the treatment of Addison's disease.

Evidence upon this point is somewhat contradictory. Nagel (1925) reported that suprarenalectomy did not reduce, but seemed to augment the pressor effectiveness of ephedrine. Chen and Schmidt (1926) stated that removal or ligation of the suprarenal glands did not diminish the pressor effect of ephedrine. It seems clear, therefore, that the circulatory effects of ephedrine are not due wholly to stimulation of the suprarenal glands.

On the other side, Suzuki (1928) found that a given dose of ephedrine produced a smaller and briefer rise in blood pressure in unanesthetized rabbits whose splanchnic nerves had been cut or whose suprarenal glands had been removed, than it did in normal controls. Section of the splanchnics reduced the effectiveness of ephedrine more than

suprarenalectomy did, which suggests that part of the influence of ephedrine upon the suprarenals must be exerted through the nervous system. Gradinesco and Marcu (1927) found that a small quantity (0.1 to 0.2 cc. of a 1 per cent solution) of ephedrine, injected directly into the suprarenal capsules of dogs anesthetized with chloroform, caused a marked and sustained rise in blood pressure. To reproduce the effect by intravenous injection of ephedrine, 7 to 10 times the quantity was required. They reported also that removal of the suprarenals led to marked reduction in the pressor effectiveness of ephedrine, which is opposed to the results reported by Nagel (1925) and by Chen and Schmidt (1926). Houssay and Molinelli (1927) employed a crossed-circulation (suprarenalo-jugular anastomosis) preparation in dogs. They reported that large doses (40 to 50 mgm. per kilogram) of ephedrine caused increased suprarenal output in six out of ten attempts. The effect was abolished by section of the splanchnic nerves, and was therefore presumably due to an action upon the nervous system—a conclusion which is like that of Suzuki (1928). It must be noted, however, that the doses of ephedrine used by Suzuki (30 mgm. per kilogram) and by Houssay and Molinelli (40 to 50 mgm. per kilogram) are so close to the toxic level that nervous effects are to be expected. Only the results of Gradinesco and Marcu point to the possibility of a suprarenal stimulation by small quantities of ephedrine, and these could scarcely be regarded as small when they were injected directly into the gland.

It appears that ephedrine is probably capable of stimulating the suprarenal glands, but whether the effect can be elicited by ordinary doses or is exerted only by toxic quantities has not been determined. It is certain that an action of this sort cannot account for all of the effects of ephedrine, for some of these are elicited upon local application (pupil), others are demonstrable in excised tissues (heart, perfused blood vessels, isolated smooth muscle). Clinical experience has shown that ephedrine has no beneficial influence upon the course of Addison's disease. However, since the pathological process is a progressive one which ephedrine could not be expected to check, this does not prove that the drug had not stimulated the residual normal tissue.

The above discussion concerning the mode of action of ephedrine can be summarized as follows:

There is no valid evidence that ephedrine is capable of directly stimulating any smooth muscle, while there is some direct evidence that it cannot do so (chromatophores of the squid, plexus-free and nicotinized intestine, albino rat uterus).

There is reason to suspect that ephedrine stimulates motor sympathetic nerves more powerfully than inhibitory ones when both are present in the same tissue (blood vessels, perhaps uterus and bladder), and possibly the inhibitory set is not affected at all by ephedrine; but when the sympathetic innervation is purely inhibitory ephedrine seems uniformly to stimulate it (bronchi, isolated sphincter pupillae, isolated intestine—nicotinized, plexus-free, sometimes intact).

Ephedrine appears to stimulate certain ganglia (cardiac accelerator, plexus of Auerbach), but whether this is a general effect or is limited to these localities has not been determined.

Its peripheral effects have not been shown definitely to involve the parasympathetic system, unless the plexus of Auerbach is regarded as a part of the latter. Ephedrine certainly has no conspicuous pilocarpine-like actions, and its important effects are not prevented by atropine.

There is no conclusive evidence that ordinary therapeutic doses of ephedrine stimulate the suprarenal gland, or that any of the effects of such doses are so caused.

The point of action of ephedrine upon the pupil appears to be central to that of epinephrine, peripheral to that of cocaine, i.e., peripheral to the finest anatomically demonstrable nerve fibers.

As to the precise mode of action, one can, in the present state of our knowledge, only characterize it by one of two general, descriptive terms—sympathomimetic or musculotropic. The first, according to the definition of Barger and Dale (1910), who introduced it, implies that the effects of the drug are analogous to those of excitation of the sympathetic nervous system by other agencies, such as electrical stimulation. The second is currently used to designate a group of drugs and poisons which stimulate smooth muscle indiscriminately and irrespective of its innervation. The outstanding example of the first group is epinephrine, while of the second pituitrin and barium are representative. In the recent investigations of ephedrine it has been tacitly assumed that epinephrine actions are the absolute

standard of sympathomimetic effects. But the originators of the term (Barger and Dale, 1910) pointed out that in some respects the effects of epinephrine are unlike those of electrical excitation of the sympathetic as well as those of many sympathomimetic drugs, notably in the pronounced tendency of epinephrine to produce inhibitory effects upon blood vessels and uterus of the cat. It does not seem to the reviewers that, with such observations on record, it is necessary to restrict the group of sympathomimetic agents to those which duplicate the actions of epinephrine in all respects.

Classification of ephedrine in one or the other of these categories is at present rather arbitrary, for the choice depends upon the definition of the terms. Since neither term is explanatory of the mode of reaction of drug with tissue substance, but is merely descriptive of observed or expected phenomena, the choice is of no great immediate importance. However, the reviewers believe that it is better at present to regard ephedrine as sympathomimetic in all its peripheral effects than to consider it as sympathomimetic in some localities, musculotropic in others. This choice is based partly upon the burden of clinical evidence, which justifies the retention of ephedrine as a drug with the general usefulness of epinephrine, and partly upon the possibility of future developments. If stimulation by ephedrine of structures that are depressed by epinephrine is conclusive proof that ephedrine is musculotropic, the matter is closed, and little or nothing has been added by way of fundamental knowledge to utilize in investigation of other substances. But if search is made for an explanation of these discrepancies upon a sympathomimetic basis, it is reasonable to suppose that something will be added to our knowledge concerning the sympathetic innervation of various structures, and it is not inconceivable that progress may be made toward an explanation of the extraordinary predilection of many substances for the sympathetic nervous system, or for certain parts of it.

It is quite possible that some of the effects of ephedrine are musculotropic. The facts remain, however, that no valid evidence exists that such is the case, that at least one of the supposedly musculotropic actions can even now be shown not to be such (i.e., the stimulant effect upon isolated intestine), and that the general picture of ephedrine actions is strikingly similar to that resulting from stimulation

of the sympathetic nervous system by other means. The reviewers therefore believe it proper to await unequivocal demonstration of musculotropic actions by ephedrine, and the exclusion of the possibility of sympathetic stimulation as an explanation, before accepting the view that any of the peripheral effects of ephedrine are not sympathomimetic.

11. Absorption and excretion

Ephedrine is readily absorbed and produces systemic effects when administered orally, subcutaneously, intramuscularly, subdurally, intraperitoneally, or rectally in animals, and the same has been shown to be true of men excepting for the subdural and intraperitoneal routes, which have not been tried. The rate of absorption in men, evidenced by the rise in blood pressure, is somewhat faster following subcutaneous or intramuscular injection than following oral administration, but the degree of effect is not significantly different (Miller, 1925); evidently absorption from the alimentary tract is complete. The effects of intravenous injection are much briefer than those of other modes of administration (Jansen). The readiness with which ephedrine is absorbed represents an outstanding and usually advantageous difference from epinephrine; it may be due to a lack of constrictor action of ephedrine upon finer blood vessels.

The fate of ephedrine in the body is still unknown, for there is no reliable and sensitive method for detecting it in tissues or excreta. It apparently passes through the liver unchanged but whether it is destroyed in the body or eliminated, in unaltered or altered form, is unknown, nor is anything known about the route of elimination.

12. Toxicity

a. Minimal lethal dose. Table 2 shows the toxicity of ephedrine in different animals. The order of the M.L.D. by different methods of administration is as follows: intravenous, intramuscular, intraperitoneal, subcutaneous, and oral. The drug is therefore most toxic by intravenous injection and least toxic by mouth. In general, different workers agree that ephedrine has a low toxicity and a wide margin of safety. In dogs, for example, the optimal pressor dose intravenously is 1 to 10 mgm. per kilogram while the M.L.D. by the same

TABLE 2

Toxicity of ephedrine in different animals

ANIMAL	EPHEDRINE	METHOD OF ADMINISTRATION	M.L.D.	AUTHOR
			mgm per kgm.	
Squid (*Loligo pealii*)...	Sulphate	Subcutaneous	10*	Nadler
Frog.....	Hydrochloride	Subcutaneous	400–500	Amatsu and Kubota
	Hydrochloride	Subcutaneous	440	Fujii
	Hydrochloride	Subcutaneous	600	Kreitmair
	Hydrochloride	Subcutaneous	540	Pak and Read
	Sulphate	Subcutaneous	530–690	Chen
Hamster.....	Hydrochloride	Intraperitoneal	350	Pak and Read
Mouse.....	Hydrochloride	Subcutaneous	500	Fujii
	Hydrochloride	Subcutaneous	1,000	Kreitmair
	Hydrochloride	Oral	3,000	Kreitmair
	Hydrochloride	Intravenous	200	Kreitmair
White mouse.....	Sulphate	Intraperitoneal	400	Rowe
Rat.....	Hydrochloride	Subcutaneous	320	Pak and Read
White rat.....	Sulphate	Intravenous	135–140	Chen
Guinea pig.....	Hydrochloride	Subcutaneous	400	Kreitmair
	Sulphate	Subcutaneous	400–425	Chen
Rabbit.....	Hydrochloride	Subcutaneous	300–460	Miura
	Hydrochloride	Subcutaneous	400–500	Amatsu and Kubota
	Hydrochloride	Intravenous	50	Kreitmair
White rabbit.....	Hydrochloride	Intravenous	50	Pak and Read
	Hydrochloride	Intravenous	60	Chen
	Sulphate	Oral	590	Chen
	Sulphate	Subcutaneous	320–400	Chen
	Sulphate	Intraperitoneal	310–400	Chen
	Sulphate	Intramuscular	340	Chen
	Sulphate	Intravenous	66–70	Chen
Gray rabbit.....	Hydrochloride	Subcutaneous	230	Pak and Read
	Hydrochloride	Intravenous	80	Pak and Read
Cat.....	Hydrochloride	Intravenous	60	Kreitmair
	Sulphate	Intravenous	75	Chen
Dog.....	Hydrochloride	Subcutaneous	220	Miura
	Hydrochloride	Intravenous	70	Pak and Read
	Sulphate	Intravenous	70–75	Chen

* Total dose.

route of administration is 70 to 75 mgm. per kilogram. It is interesting to note the great deviation of the M.L.D. in mice obtained by Kreitmair from those reported by Fujii and by Rowe. The difference by subcutaneous injection is fully 100 per cent or more. One wonders if these three workers experimented on the same species of animals. The variations in the results, not more than 10 to 20 per cent among other investigators, should not be considered significant if one bears in mind the errors in the determination of toxicity. Such errors have been critically analyzed by Trevan (Proc. Roy. Soc., 1927, B, ci, 483) and by Burn (Methods of Biological Assay, London, 1928).

b. Toxic symptomatology. Miura (1887) briefly described the toxic signs in animals with lethal doses of ephedrine. He observed general depression, mydriasis, stoppage of the respiration and diastolic standstill of the heart in frogs. The signs of poisoning in mice, rabbits and dogs, as stated by him, are mydriasis, elevation of temperature, acceleration of the pulse and respiratory rates, fall of blood pressure, clonic convulsions and death due to cardiac and respiratory failure. Amatsu and Kubota (1913) reported about the same results. More detailed investigations were carried out by Chen on frogs, rats, guinea pigs, rabbits, cats and dogs. In his experience, cardiac collapse occurs sooner than respiratory failure. Animals poisoned by sublethal doses of ephedrine recover without complications. A full account of poisoning symptoms in frogs, mice, guinea pigs, rabbits and cats is also given by Kreitmair.

The picture in the squid, described by Nadler, may be worth mentioning. Ten milligrams of ephedrine given subcutaneously frequently cause gangrene and necrosis at the site of injection, leaving the muscles of the mantle exposed. The animal may, however, live for hours. Oral administration and injection into the circulation via the heart, in 5 to 10 mgm. dosage, produce a dark coloration. In these cases the arms are extended and limp, and on stimulation they go into a series of tonic contractions. The respiratory movements are faster and heavier, gradually become slower and labored, and death occurs.

c. Repeated administration. In a series of rabbits Chen gave daily doses of ephedrine for several weeks intravenously, intramuscularly and orally and reported that the drug produces no observable toxic

effects. These animals gained in weight as steadily as the controls. Upon sacrifice, there were no gross or microscopic lesions in the visceral organs. No tolerance is developed to the mydriatic or pressor action of ephedrine by repeated administration, nor is there any change in the dose required to cause death. Similar results were obtained in rats. This work has recently been verified by Doty.

IV. CLINICAL APPLICATIONS

1. Methods of Administration and Dosage

For systemic effects, ephedrine can be given by mouth, by subcutaneous or intramuscular injection, and only exceptionally by intravenous administration. On occasion, the drug may be used per rectum, as shown by Thomas and by Hess. For local application to the nasal mucous membrane, concentrations varying from 1 to 5 per cent can be used. It may be in the form of a solution, pure or mixed with other aromatic ingredients, a jelly or a snuff. As a mydriatic, ephedrine is used in 5 to 10 per cent aqueous solutions.

As regards the dosage for internal administration, this is governed entirely by the development of untoward symptoms. A small dose for one individual may be a large one for another. From the experience of early investigators, a single dose may be 50 to 100 mgm. for an average adult. Hess advocates the use of 1 to 2 mgm. per kilogram of body weight. This dose appears to be slightly too large, especially for ambulatory patients, judging from the frequent occurrence of side reactions. It has now been reduced to 25 to 50 mgm., and may be repeated as needed. It can be given three or four times a day.

In children from 2 to 14 years of age, Munns and Aldrich use 12 to 50 mgm. of ephedrine by mouth. Anderson and Homan employ $\frac{1}{4}$ grain (15 mgm.) for those over 1 year of age and $\frac{1}{8}$ grain (7.5 mgm.) for those under 1 year, the drug being given in water solution. Stewart prescribes $\frac{1}{6}$ grain (10 mgm.) in children from 1 to 5 years, $\frac{1}{4}$ to $\frac{1}{2}$ grain (15 to 30 mgm.) from 5 to 6 years, $\frac{1}{8}$ grain (7.5 mgm.) from 6 to 12 months, and $\frac{1}{12}$ grain (5 mgm.) under 6 months of age. Such doses are given with 20 minims of glycerine and enough chloroform water to make a dram (4 cc.).

2. Side effects

The untoward symptoms of ephedrine, given orally, subcutaneously or intramuscularly, have been recorded by T. G. Miller, Rowntree and Brown, Gaarde and Maytum, Pollak and Robitschek, MacDermott, Hollingsworth, Thomas, Balyeat, Berger and Ebster, Althausen and Schumacher, Wu and Read, Anderson and Homan, Kesten, Middleton and Chen, Wilmer, Gay and Herman, Bloedorn and Dickens, Boston, Long, Ségard, Chopra, Dikshit and Pillai, Higgins, and Stewart in connection with their clinical investigations. The development of such symptoms and signs depends upon the dosage but more upon the stability of the nervous system, as emphasized by Pollak and Rabitschek. Similarly, Gaarde and Maytum state that the occurrence of the nervous smptoms bears a distinct relationship to a neurotic tendency and the daily activity of the individual. The same therapeutic dose, therefore, may produce only desirable effects in one patient, and equally beneficial results but with some discomfort, in another. Meals sometimes aggravate the symptoms (Middleton and Chen). It is the best plan to test out the sensitivity of the patient with small doses, say 10 mgm., and establish the maximal tolerated dose. It is only by experience and judgment that these side reactions can be reduced to a minimum.

Subjectively, the common symptoms are palpitations, trembling, weakness, sweating, feeling of warmth, chilly sensation, nausea, and vomiting, while those of less frequent and rare occurrence are nervousness, headache, insomnia, dyspnea, a tired feeling, thirst, drowsiness, precordial pain, feeling of distress in the precordium, flushing of the skin, tingling and numbness of the extremities, anorexia, constipation, quivering feeling, faintness and diuresis. Boston makes a special report of difficulty in urination in 6 cases he observed. Berger and Ebster give an account of a neurotic patient who had colic, followed by diarrhea and anorexia, after the use of ephedrine, and of still another who had such an increase of libido that he called ephedrine an aphrodisiac. Higgins reports a case of chronic ephedrine poisoning which simulated hyperthyroidism.

Objectively, the common signs are diaphoresis, tremor, extrasystoles and tonal arrhythmia, while those of less frequent or rare occurrence are tachycardia, restlessness, mydriasis, albuminuria, appearance of

red blood corpuscles and casts in the urine, and decompensation in organic cardiac disorders. Anderson and Homan observed abdominal distension, pain and discomfort, discharge from the nose and apparent suppression of urine. T. G. Miller recorded a case of myocardial degeneration in which ephedrine caused pulsus alternans. Four out of 11 cases in the series of Middleton and Chen showed after ephedrine extrasystoles of ventricular or auricular origin, as shown by electrocardiography. Another case developed a paroxysm of tachycardia which lasted for a few minutes. Bloedorn and Dickens describe a case of cardiac asthma, diagnosed as bronchial asthma, which resulted in cardiac embarrassment, including pulsus alternans, marked tachycardia and cardiac decompensation, following ephedrine therapy. Such dangerous effects, however, do not appear to occur very frequently, for in the series of Hess and of Gay and Herman there were several patients with myocardial insufficiency but none experienced any harmful effects. Pennetti observed, by means of electrocardiograms, that ephedrine increased the frequency of pre-existing extrasystoles in 2 cases but produced no change in a case of A-V block of vagal origin. The block in the last case disappeared after the administration of atropine or epinephrine.

All the side effects occur singly or in groups of but a few, become most pronounced when the systolic blood pressure is at its highest level, and disappear as the pressure returns to normal. Some of the subjective symptoms may be explained by the pharmacological action of the drug. For example, palpitation is due to circulatory changes, as borne out by objective observation, and the insomnia and tremors present in some cases are due to stimulation of the central nervous system. Leake, Loevenhart and Muehlberger attribute the headache under ephedrine to the changes in pressure in the arteries or veins within the skull. Occasionally, the untoward symptoms in some individuals disappear on repeated administration of ephedrine, showing that these individuals become better accustomed to the drug. Althausen and Schumacher mention two such cases and Hollingsworth another.

Investigators seem to agree that the prolonged use of ephedrine does not have any cumulative harmful effects and does not result in habit formation. Middleton and Chen reported a case that received a

total quantity of 10 grams of ephedrine sulphate in a period of 11 days but showed no detectable pathological changes. Withdrawal did not give that patient any discomfort or any craving for the drug. Wu and Read mentioned a case in which ephedrine therapy (40 to 60 mgm. every 1 to 3 days) was continued for three years. Laboratory examinations did not show any ill effects. Thomas and Balyeat, and Collina also express the opinion that ephedrine is not a habit-forming drug. In 5 out of 51 cases of asthma and hay fever, Althausen and Schumacher noted a considerable diminution of action in the relief of attacks, showing the increase in tolerance by repeated administration. It should also be borne in mind that the attacks may not have been of equal severity and that severe cases are unfavorable for the action of ephedrine.

Contraindications are but few. In all cardiac disorders, especially with signs of decompensation, ephedrine should be used with caution. Ségard mentioned angina and hypertension as contraindications of the use of ephedrine. However, recent work on spinal anesthesia shows that it is permissible to use ephedrine in hypertension cases. Care should also be taken in cases where there is a labile vagosympathetic equilibrium, although there is not the same extent of hypersensitiveness to ephedrine as to epinephrine in Graves' disease (Csépai and Fernbach). In late acute circulatory collapse, it is best not to give ephedrine, since it may be a dangerous procedure, as shown by Blalock in experimental animals.

Pitkin mentions two fatalities in spinal anesthesia which were attributed to 50 mgm. of ephedrine, but his own toxicological studies do not seem to support this statement. Sise knows of two similar cases, not of his own; each patient was in very poor general condition, received repeated doses of ephedrine, totaling about 150 mgm., became cyanotic, fibrillated and, although the pressure was at or above normal, died in about 12 hours. In experimental animals, however, death never occurs if the blood pressure is at its normal level.

V. THERAPEUTIC USES

1. In asthma

Following the publication of T. G. Miller, who first employed ephedrine in the treatment of bronchial asthma, many other investi-

gators have made similar reports concerning their experience with the drug. It appears to be generally agreed now that ephedrine is a good palliative remedy in the treatment of bronchial asthma. Its action is weaker than that of epinephrine, and it is therefore only occasionally efficacious in severe attacks of asthma. In mild and moderate cases it may prevent the attack if it is given several hours beforehand, abort the attack if it is administered during the prodromal period and sometimes stop the attack when it is used while the attack is in progress. Its prophylactic action seems to be better than its antispasmodic property. This is well illustrated by the work of Vallery-Radot and Blamoutier, who showed that ephedrine was effective in 16 (69 per cent) out of 23 cases when given prophylactically but in only 17 (43 per cent) out of 39 cases when given during the attack. Leopold and Miller show that the best results are obtained in allergic and reflex nasal cases, and comparatively less satisfactory results are obtained in the infectious type. Similarly, Gay and Herman note that the relief from an asthmatic attack is most quickly obtained in patients whose symptoms are due to a specific foreign protein, such as pollens, animal emanations, orris root, feathers, with or without secondary bronchitis. According to Thomas, a field for the use of ephedrine appears to lie in its employment as often as necessary to prevent the occurrence of paroxysms in asthmatic patients who are awaiting the completion of skin tests, courses of vaccine administration, rhinological treatment, radiotherapy or other methods from which more permanent benefit is hoped for. This author adds, however, that patients who are about to undergo sensitization tests should be cautioned not to seek relief in ephedrine within a period of 12 hours before such tests are to be made, for the drug, like epinephrine, temporarily prevents the appearance of positive reactions to specific tests for sensitiveness.

When desirable effects occur, ephedrine has certain advantages over epinephrine from the therapeutical point of view. In the first place, it can be given by mouth; secondly, it can be employed as a preventive; thirdly, it has a more prolonged action, although its onset is not so prompt; and fourthly, it produces less side reactions. Some individuals who are unable to take epinephrine are fortunately able to use ephedrine without untoward symptoms. In other words, a reaction from epinephrine does not indicate that ephedrine likewise will have a

TABLE 3

Results of ephedrine therapy in the treatment of asthma

AUTHOR	NUMBER OF CASES	RESULTS
T. G. Miller (1925).	7	Benefit in 6; none in 1
T. G. Miller (1926)	36	Good results in 26, relief not marked in 4; no improvement in 6
Leopold and T. G. Miller (1927)	59	Complete relief in 33; partial relief in 17, no relief in 9
Thomas (1926)	20	Relief in 17
Thomas (1927)	Over 300	Ephedrine is a remarkably efficient drug
MacDermott	20	Relief in most cases
Pollak and Robitschek.	16	Ephedrine replaces epinephrine injections
Hess	15	Very good in part, good in part; rarely insufficient success
Heller	1	Marked improvement (observation made on himself)
Jansen	?	Favorable
Kammerer and Dorrer	9	Relief in 8; none in 1
Middleton and Chen	25	Relief in 9; improvement in 8; inconclusive in 8
Piness and Miller	110	24 severe cases did not obtain relief
Althausen and Schumacher.	39	Complete relief in 21; partial relief in 15
Wilmer	100	Relief in 75; relief in severe attacks, 10
Wilkinson	12	Excellent
Wu and Read.	(Ward) 11	9 responded well
	(Ambulatory) 90	Favorable
Bibb	2	Perfect relief
Balyeat	Over 100	Ephedrine is of considerable value in 65 per cent of the cases
Rudolf and Graham	(Severe) 2	Ephedrine reduced epinephrine injections in one, but had no effect in the other
Jankowski	11	Ephedrine has a marked effect
Collina	14	Complete relief in 5, evident improvement in 5; temporary improvement in 2; no change in 3
Taylor	10	Prompt relief in every case

TABLE 3—*Concluded*

AUTHOR	NUMBER OF CASES	RESULTS
Gay and Herman	100	Complete relief in 71; moderate relief in 21, no relief in 8
Vallery-Radot and Blamoutier	49	In 23, ephedrine used prophylactically, produced benefit in 16 but none in 7; in 39 ephedrine given during the attack, gave relief to 17, but none to 22
McPhedran	12	Complete relief in 9; partial in 2
Ségard	?	Total relief in mild cases
Long	?	Effective in relief and prevention
Munns and Aldrich	(Children) 22	Complete relief in 12; partial in 4; none in 6
Anderson and Homan	(Children) 5	Marked relief
Stewart	29	Relief in over half

similar unpleasant effect. A combination of epinephrine and ephedrine has been found efficacious by some and objectionable by others. On the whole, if the patient shows reactions to epinephrine alone, or to both epinephrine and ephedrine, the injection of epinephrine in the presence of ephedrine usually exaggerates the untoward symptoms (Althausen and Schumacher, and Haintz). If the patient can tolerate both drugs well, there is no reason why epinephrine cannot be given in addition to ephedrine if the latter fails to act.

Relief from ephedrine takes place in 20 to 30 minutes if it is given by mouth but in 10 to 15 minutes if it is administered intramuscularly or subcutaneously. The clinical improvement can sometimes be observed objectively. It consists in diminution of cyanosis, increase of vital capacity, decrease of râles, gradual disappearance of orthopnea, and euphoria of the patient. Subjectively, the patient usually volunteers the information that he can breathe better and feels relieved. The relief may be followed by coughing and expectoration (Heller). Individuals who suffer regularly from daily or nightly paroxysms may remain asthma-free for long periods of time by taking the drug once, twice or three times every 24 hours. They can resume their daily activities and pass comfortable nights. Withdrawal of the ephedrine results in recurrence of asthmatic symptoms. Other persons are not

so fortunate, for the by-effects, occasionally met with, render its use impracticable even though it relieves the bronchospasm.

In children afflicted with asthma the same beneficial results have been obtained with the proper doses of ephedrine, as reported by Munns and Aldrich and by Anderson and Homan.

The results of various workers, not only in this country but in various parts of the world, are summarized in table 3. It will be seen that beneficial results have been obtained in the majority of cases by each physician. It is futile to compare the percentage of improvement in different series since the essential factor is not the patient or the drug but the severity of the asthmatic attack.

2. In hay fever

Gaarde and Maytum in 1926 reported their first series of 26 cases of autumnal hay fever which were treated by the oral administration of ephedrine. Thirteen of these patients obtained complete or almost complete relief from symptoms by taking 60 mgm. doses 2 to 3 times every 24 hours. The relief lasts 3 to 7 hours after each dose. Excessive nasal secretions stop, ocular symptoms disappear, and in every way the patients are entirely comfortable. In 5 cases the result was fair and partial relief was obtained for 2 to 3 hours after each dose. In 8 cases the results were negative. In their next series, published in 1927, they made a comparison of the effects of oral administration with those of a 3 per cent nasal spray. In 24 patients who received ephedrine by mouth, 13 (54 per cent) were completely or almost completely relieved for 4 hours or more; 7 (29 per cent) were partially relieved; and 4 (16 per cent) were not relieved or they were not able to tolerate the nervous symptoms. In a similar series of 25 cases which were given ephedrine by a spray, 7 (28 per cent) were markedly relieved for several hours; 12 (48 per cent) were partially relieved for several hours or completely relieved for less than an hour; and 6 (24 per cent) were not benefited. Ephedrine given in 3 per cent solution as a nasal spray, therefore, appears to be less efficacious and the relief is of shorter duration. However, the majority of patients feel that its use adds to their comfort. The best results are obtained when the spray is used early in the paroxysm. The effect of both the local and internal administration seems to depend on the severity of the paroxysms and

the good results are obtained in the milder seizures. Untoward symptoms, when they occur, are attributable to the neurotic temperament and nervous state of the patient. In analyzing their data of two successive seasons, Gaarde and Maytum conclude that ephedrine should be given a definite place in the treatment of autumnal hay fever, and they emphasize the fact that when good effects are obtained they are temporary and symptomatic. Leopold and Miller observed complete temporary relief in 63 per cent of 11 cases and prefer the oral route for the administration of ephedrine. Encouraging results in the treatment of hay fever with the new drug are also noted by Thomas, Balyeat, Althausen and Schumacher, Wilkinson, and Ramirez. Piness and Miller observed relief in only 1 out of 5 cases when ephedrine was given by mouth, but in 18 out of 20 cases when the drug was used as a spray. These results show that local application is more efficacious than oral administration.

3. In bronchitis and emphysema

In 11 cases of senile emphysema, 1 with active and 6 with inactive pulmonary tuberculosis and all having hypotension, Saxl reports that ephedrine produced a striking improvement of the dyspnea in 8 but had no effect in 3. The blood pressure rose 15 to 30 mm. Hg for several hours with 100 mgm. doses. According to him ephedrine has the advantage over atropine in that it does not cause dryness of the throat. These conclusions have been confirmed by the study of a larger series of cases by himself.

4. In whooping cough

Anderson and Homan were the first to try out ephedrine therapy in pertussis. They noticed that the drug abolished the characteristic signs of whooping cough in 18 out of 20 children. In all instances in which improvement occurred, some cough remains but in mild form and of a type associated with acute upper respiratory infections. They believe that ephedrine is most useful during the second stage of the disease. In a series of 35 children suffering from pertussis Stewart observed that ephedrine relieves the coughing, the whooping and vomiting in mild and moderate cases. In severe cases there is no effect at all. He states, however, that the drug, combined with

belladonna and ipecac, seems to have a beneficial effect. The progress of the infection is not in any way influenced.

5. In spinal anesthesia

The blood pressure-raising property of ephedrine appears to be most useful in spinal anesthesia. Rudolf and Graham studied 26 cases under spinal anesthesia, in the surgical and gynecological wards of a hospital, in which they administered ephedrine intravenously. Their results are striking, especially with reference to the elevation of the blood pressure. In their first few cases the blood pressure was allowed to drop until it had apparently reached its lowest level and then 50 to 100 mgm. of the drug were given by vein. With but one exception there quickly resulted an extraordinary and prolonged rise in blood pressure, with a slower and stronger heart beat. This lasted for 1 to 1½ hours. In their later cases they used smaller doses and gave the ephedrine within 2 to 3 minutes after the anesthetic, so as to anticipate the fall rather than combat it after it had developed. This improved technique proved to be satisfactory and they had no case of drastic fall in blood pressure or of vomiting, which occurs frequently in spinal anesthesia. They also state that the drug can sometimes be given with advantage before the spinal anesthetic where the blood pressure is already too low. Ockerblad and Dillon have used ephedrine in 50 to 100 mgm. dosage, subcutaneously or orally, in a series of 250 cases and have been successful in restoring the right amount of arterial tension necessary for surgical operations and the well being of the patient. The fall in pressure must be anticipated if the best results are to be obtained with ephedrine. In other words, once the pressure falls as much as 50 per cent, the return to the normal level—even under comparatively large doses of the drug—is slow and uncertain. It is better to reinforce the vascular system with ephedrine before the actual administration of the spinal anesthetic, to have the blood pressure 20, 30 or more millimeters Hg above the normal for that individual. The drug is repeated if there is a tendency to fall. Chronic hypotension, which used to be a contraindication to spinal anesthesia, is no longer a valid objection. Ephedrine relieves any tendency toward retching and vomiting which, according to Ockerblad and Dillon, is due to the preliminary hypodermic injection of morphine

and scopolamine. Pitkin uses 1 to 1.3 cc. of a solution containing 1 per cent of novocaine and 3 per cent of ephedrine to make a wheal at the site of, and before, lumbar puncture. He is satisfied with the pressor action of ephedrine and performs operations below the diaphragm. He states that the action of the drug can be relied on for 2 to 3 hours and has contributed much to the safety of spinal anesthesia. Pitkin and McCormack, and Cosgrove have tried the drug in obstetrics where spinal anesthesia may be indicated, as in low forceps extraction, episiotomy, perineorrhaphy, dilatation or incision of the cervix, podalic version, craniotomy and extraction, vaginal hysterectomy, etc. Ephedrine is used prophylactically as outlined by Pitkin. Holder gives ephedrine subcutaneously 15 minutes before the administration of the spinal anesthetic and succeeds in keeping the systolic blood pressure at a constant level, although somewhat below the original. In 151 cases, approximately one-half received ephedrine (50 to 100 mgm.) and the average drop of blood pressure was 12.8 mm. Hg. In the other half the average drop of pressure was 37.5 mm. Hg. Wehrheim reports his experience in over 300 cases of spinal anesthesia with ephedrine (50 mgm.) injected subcutaneously 5 minutes before the spinal tap. To show the benefit of this procedure, he states that the average drop in blood pressure in spinal anesthesia without ephedrine is 10 to 30 mm. Hg within 15 minutes, but the average drop in 30 consecutive medicated cases was nil. Sise considers the repeated injection of ephedrine unnecessary and sometimes dangerous if the blood pressure begins to drop in spite of the use of ephedrine. Other measures, such as saline infusions with small doses of epinephrine, should be resorted to. Other favorable reports of spinal anesthesia with ephedrine have been made by Babcock, Wallace, Jeck in kidney and ureter operations, DeCourcy, Case who uses the drug subcutaneously immediately after the spinal injection, Gosse, Saklad, and Russell who injects ephedrine intramuscularly before the spinal puncture.

6. In hypotension

The use of ephedrine in the treatment of chronic or subacute hypotension has, with some exceptions, not proved as promising as had been hoped for. It has been tried in Addison's disease. Chen and Schmidt

mentioned a single case in which ephedrine seemed to have a good effect. T. G. Miller studied two cases of early Addison's disease and found a rise of blood pressure and increase of basal metabolic rate following the administration of ephedrine, but both patients died from the disease. Rowntree and Brown treated 14 cases of Addison's disease and two of questionable Addison's disease with ephedrine. They also demonstrated a definite rise of blood pressure and increase of metabolic rate, but the rise was not accompanied by a marked feeling of well being, significant increase in strength or relief from the gastric symptoms or circulatory asthenia. Only in one case of early Addison's disease excellent clinical results were obtained. The feeling of weakness and exhaustion disappeared and the patient felt buoyant, strong and refreshed.

T. G. Miller tried ephedrine in a number of cases with essential or chronic hypotension and observed that in some of them it produced a temporary elevation of pressure, lasting from 3 to 6 hours after each dose by mouth. The response in pressure increase was not as striking as in certain other types of cases, and sometimes a dose of 50 mgm. had no effect whatever on the hypotension, yet most of the patients expressed themselves as feeling stronger and more energetic under its influence. Rowntree and Brown administered ephedrine in 9 cases of nervous exhaustion and hypotension. Aside from the rise of blood pressure for 3–6 hours and some increase of the basal metabolic rate, no other evidence of clinical improvement was observed objectively, although some of the patients were convinced that they felt somewhat stronger. Pollak and Robitschek mentioned a case of pneumonia in which daily doses of ephedrine raised the blood pressure from a level below 100 mm. to 145 mm. Hg, although accompanied by some untoward symptoms. Hess reported a series of cases with hypotension, including pneumonia, bronchopneumonia, pulmonary tuberculosis, cardiac insufficiency and vasomotor weakness. Repeated small doses of ephedrine produced favorable results. In the treatment of paresis with malarial fever, the drug can maintain the blood pressure at the normal level, as shown by three cases. He advocates the combination of ephedrine with atropine in the treatment of bronchial asthma and with digitalis or caffeine in cardiac insufficiency with low pressure and chronic bronchitis. Middleton and Chen studied three

patients who had hypotension—two with asthma and one without asthma—with ephedrine at frequent intervals for a considerable length of time, in the hope of elevating their blood pressure and maintaining the higher pressure. The results in two were practically negative. The slight elevation in the third was probably due to the improvement of his asthmatic condition under ephedrine therapy. Wu and Read, on the other hand, state that they obtain very satisfactory results with ephedrine in cases of hypotension. Althausen and Shumacher determined the value of ephedrine in 7 patients with chronic hypotension. During an average period of 20 days the blood pressure was raised by daily doses of the drug and three patients felt stronger while four did not notice any change. Ghrist and Brown reported an interesting case of postural hypotension with syncope, in which ephedrine raised and sustained the blood pressure and rendered the patient free from symptoms. He has been able to go back to work without further attacks by the daily use of the drug. These authors believe that ephedrine may exercise a specific alleviative effect on the disease.

7. In shock

In acute circulatory collapse it is still a question how much good ephedrine can do. The drug is not indicated in late stages of shock. Chen in dogs observed that ephedrine restores the blood pressure in hemorrhage and in experimental shock induced by histamine, peptone, anaphylaxis or surgical manipulation, and that it fails to act when the heart beat becomes impaired or respiration ceases, or the degree of shock is too extensive, or when the hemorrhage exceeds 25 per cent of the total blood volume. Blalock, also experimenting with dogs, concluded that in less severe cases of shock ephedrine works better than caffeine, strychnine, epinephrine and digitalis, but in severe cases it seems to hasten death. Chen and Schmidt investigated its effect in surgical shock in a single patient, with encouraging results. Miller reported real improvement in two cases in profound shock. In one of them an intravenous injection of 100 mgm. raised the blood pressure from practically zero to 65 mm. Hg, although the patient finally died of general peritonitis. Since then, he has tried the drug in a large number of cases of shock and hemorrhage, usually without beneficial result, even though the drug was given intravenously (unpublished).

Pollak and Robitschek recorded a case of acute alcoholic poisoning in which ephedrine caused a definite increase in blood pressure from an almost imperceptible pulse. Similarly, in a patient dying of post-operative peritonitis Rudolf and Graham administered 100 mgm. of ephedrine intravenously. The systolic blood pressure rose from an unrecordable level to 86 mm. Hg. within 2 minutes and later to 130 mm. Hg. The good effects lasted for some 45 minutes and then the patient gradually sank and died some five hours later. Althausen and Schumacher reported two cases in a state of surgical shock in which ephedrine was given. One of them rapidly recovered and the other died. Both were given blood transfusions simultaneously. Waters (cited by Jackson) believes that the chances for a favorable result from the action of ephedrine are much increased if it is given in the early stages of traumatic or surgical shock. H. Schmidt advocates the use of ephedrine as a prophylactic measure against vascular shock in local anesthesia and surgical shock in major operations under chloroform, spinal or avertin anesthesia. The action usually lasts longer than the operation.

8. In Adams-Stokes' syndrome

In a single case of complete heart block T. G. Miller gave a subcutaneous injection of 100 mgm. of ephedrine: it caused an increase of the ventricular rate from 38 to 55 per minute, of the auricular rate from 110 to 125 per minute, accompanied by a rise of blood pressure, as shown by electrocardiograms. The shape of the P-wave and the ventricular complexes was observed to alter from time to time. Hollingsworth was the first to report a case of Adams-Stokes' syndrome in which the first dose of ephedrine (50 mgm.) by mouth stopped the attacks within 30 minutes. The latter did not recur in 36 hours. On taking the drug every morning the patient was completely freed from symptoms and was able to resume her household duties. After three weeks the drug was withheld but the attacks recurred in 48 hours. It was therefore resumed. Stecher reported a similar case of complete heart block with syncope and convulsions in which ephedrine gave complete relief. The patient was given 30 mgm. doses three times a day during the first week and 20 mgm. doses three times a day during the next two weeks. The drug was then discontinued and the patient

had no further attacks for 10 weeks afterwards, during which time he was ambulatory.

9. As a nasal astringent

Dr. Alice H. Cook (cited by Fetterolf and Sponsler) was the first to use ephedrine locally in the nose and throat. She found that a 10 per cent solution of ephedrine causes almost instant shrinkage of an engorged nasal mucous membrane and that the action is more rapid and complete than that of a 4 per cent solution of cocaine. This subject was investigated more thoroughly by Fetterolf and Sponsler who used a 5 per cent solution in 17 patients and found it so effective that they described ephedrine as a drug which, for use in the nose, has all the advantages of epinephrine with perhaps none of its disadvantages. Following the application to the anterior part of the lower turbinate by means of a cotton brush, contraction begins in from a few seconds to one minute. The maximum is established in from 1½ to 5 minutes or in an average time, for their series, of 2⅓ minutes. In spite of a small area of application the turbinate in every case contracts throughout its entire length. The general outline of the medial surface changes from convex to concave. Contraction is so complete and the mucosa becomes so thin and flat that it fits the bone as a glove fits the finger. The color is altered to a paler hue and assumes a gray tint at the maximum of the action. No white ischemia occurs, as is often seen with epinephrine. Relaxation begins in 2 hours and 35 minutes and is complete in an average time of 3 hours and 17 minutes. There is no sign of irritation of the mucous membrane, such as sneezing, either on the same day or the following day. There is no secondary congestion, as with epinephrine. Similar favorable results have been obtained with weaker solutions (1 to 3 per cent) by Fiske, Proetz, and others. Kennon advocates the use of ephedrine in (1) acute nasal accessory sinus disease, (2) chronic nasal sinus disease where surgery is contraindicated and as an adjunct to surgery, and (3) chronic accessory sinus disease in children where surgery should be used only for the removal of toxic foci. Merkel states that a 3 per cent solution of ephedrine is just as effective as a 5 per cent solution in rhinotherapy and the drug can be applied by (1) spraying, which is best for children, (2) topical application with cotton on a probe, and (3) introduction

into the nose on cotton packs. Fifteen infants having definite evidence of ethmoiditis were treated by this author in the following manner: the nose was irrigated with a warm saline solution twice daily; half an hour after the irrigation a 2 per cent solution of ephedrine was sprayed on the nasal mucosa; and 5 minutes later 3 drops of a 5 per cent solution of argyrol were placed in the nostril. Twelve patients at least were benefited by such a régime. Ephedrine does not need to be in contact with the nasal mucosa for more than a few seconds. A pack left in situ for 3 minutes causes no more contraction than after a shorter time. Daily use over a period of 10 days shows no change in the rapidity or duration of the action. The drug brings about free ventilation and drainage for a period of 3 to 6 hours. Merkel also tried ephedrine in 3 cases of epistaxis and claimed to obtain good results. Reaves, employing a mixture of 1 per cent of ephedrine and 0.5 per cent of butyn, performs minor surgical operations on the nose. Gaarde and Maytum reported that ephedrine given orally produces a stoppage of excessive nasal secretions in cases of hay fever. They noticed sneezing in some patients. Leopold and Miller observed actual shrinkage of the nasal mucous membranes in similar cases by the same method of administration. In experimental animals (dogs), a contraction of the nasal mucosa and accessory sinuses following the intravenous injection or local application of ephedrine has been demonstrated by Rudolf and Graham with Copeland's technique, by Jackson with his own device and by King and Pak with Tschalussow's nasal plethysmograph.

10. As a mydriatic

The first ophthalmological work with ephedrine was done by Miura in 1887. He observed that a 6 to 7 per cent solution of ephedrine produces mydriasis in most people in from 40 to 60 minutes. The use of a 10 per cent solution in 18 patients did not cause a maximal dilatation of the pupil but produced sufficient dilatation for the visualization of the retina. During dilatation the light reflex is retained and the accommodation is not paralyzed. There is no increase in intra-ocular pressure, no irritation or inflammation follows its instillation and no ill effects result from prolonged use. One patient receiving three treatments daily for 15 days showed no pathological changes. The dura-

tion of mydriasis varies from 5 to 20 hours. Children and aged people are more susceptible than young adults. The diseased iris does not seem to respond well. De Vriesse published practically identical results in 1889. Inouje encountered a case in which the instillation of ephedrine precipitated an acute attack of glaucoma. Groenouw reported 100 cases he studied in which the following mixture was used: ephedrine hydrochloride, 1 gram; homatropine hydrochloride, 0.01 gram; and water, 10 cc. Merck named this mixture *Mydrin*. The mydriasis with this combination begins in 8½ minutes, reaches its maximum in 34 minutes and lasts for from 4 to 6 hours. The accommodation is not interfered with by this solution. In strong light the pupil contracts to 5.6 mm. in diameter. Similar favorable results have been reported by Suker, Snell, Cattaneo and Stephenson. Marmoiton not long ago (1911) gave a résumé of this work on ephedrine. All these authors advocated the use of ephedrine in the exploration of the fundus on account of the rapid action, absence of cycloplegia, short duration of mydriasis and harmlessness of the drug. Since the recent extensive study of ephedrine interest in its use in ophthalmology has been revived. Middleton and Chen observed that a 10 per cent solution of ephedrine, or the same concentration with the addition of 0.1 per cent of homatropine or of 0.1 per cent of atropine, may be used locally as a mydriatic for routine ophthalmoscopic examinations. Chen and Poth found that ephedrine is an efficient mydriatic for Caucasians but is of little value in dilating the pupil of the Chinese and of negroes. The investigation was made both in diffuse daylight and under controlled illumination with accurate measurements. The same difference in mydriatic action in these three races was observed with cocaine and euphthalmine, which have hitherto been used indiscriminately in clinics. The question seems not to be entirely one of different amounts of pigmentation, as rabbits of various colors respond almost equally to ephedrine applied to the conjunctival sac. Howard and Lee also reported that ephedrine is more effective as a mydriatic in individuals with light irides than in those with dark. Dittmann, on applying a 3 per cent solution on himself, experienced conjunctivitis, increased tension and blurring of vision. Schoenberg, on the other hand, concluded, from a study of several hundred patients, that a 1 to 3 per cent solution of ephedrine is a valuable drug to produce

mydriasis for ophthalmoscopic examination. The same author observed that the effect of ephedrine on the human pupil is counteracted by pilocarpine within 5 to 10 minutes. Similarly, Müller, after 2½ years' experience, considers it as a useful agent for diagnostic purposes. This investigator administered ephedrine in several cases of chronic glaucoma and found no change in the intra-ocular pressure. Recently, Chen and Poth found that the dilated pupil in Caucasians under the influence of ephedrine is made more stable to light if a small amount of homatropine or euphthalmine is added. The mixtures have a short duration of action and some (but only little) influence upon the accommodation. As a result a better view of the eye ground is obtained without inconveniencing the patient by blurring of vision. The solutions are but little irritating. Some subjects experience a burning sensation which lasts for about 30 to 60 seconds. In uveitis and iritis, however, ephedrine, or its mixtures with other mydriatics, fails to dilate the pupil.

11. As an antidote for narcotic drugs

C. F. Schmidt observed in experimental animals that ephedrine possesses the power not only to increase the O_2 supply of the brain by its pressor action but also to stimulate the respiratory center directly. He advocates the use of ephedrine and epinephrine in serious depression or failure of the respiration, such as following morphine, in preference to the conventional respiratory stimulants, as caffeine, atropine, strychnine or camphor. Similarly, Kreitmair found that in rabbits and cats ephedrine, given intramuscularly or intravenously, not only restores the respiration after its paralysis by scopolamine but also raises the blood pressure. He suggests its clinical use in twilight sleep with scopolamine and morphine, or scopolamine and eucodal (dihydroxycodeine hydrochloride). Subsequent reports seem to bear out his point. In psychiatry Guttmann used hypodermically ampules containing 1 mgm. of scopolamine and 25 mgm. of ephedrine in all cases of senile dementia, arteriosclerosis and 2 excited cardiac psychoses. During sleep these individuals had a quiet smooth breathing instead of snoring. The addition of ephedrine apparently does not affect the narcotic action of scopolamine. In surgery, Streissler reported 26 cases in which he injected subcutaneously morphine and ampules

containing 1 part of scopolamine and 25 parts of ephedrine to produce analgesia and anesthesia. These drugs are given in divided dosage. According to Streissler, 2½ hours before the operation the patient should be given 10 mgm. of morphine and 1 mgm. of scopolamine with 25 mgm. of ephedrine. After 15 minutes 10 mgm. of morphine are given and 15 minutes later 1 mgm. of scopolamine with 25 mgm. of ephedrine is again injected. If sleep is not deep 1½ hours before operation, 0.5 to 1 mgm. with ephedrine, which is an extra dose, should be given. Finally, ½ hour before operation, 10 mgm. of morphine, together with 1 mgm. of scopolamine plus ephedrine are injected. With these medications the pain sensation disappears before tactile sensation. There is no anxiety, fear or resistance on the part of the patient during induction of anesthesia. Many operations can be done under this form of analgesia and anesthesia, such as amputations of the breast, surgical treatment of the stomach or gall bladder, etc. In young vigorous persons ether may be given during the operation, but only as little as possible. The pulse rate is often unchanged but is usually accelerated after the operation. Respiration is slowed but not made stertorous. The blood pressure remains elevated for two hours after the operation. The patient wakes up in 4 to 6 hours with complete amnesia and euphoria and without any struggling. Vomiting does not occur. The pain in the wound is not so severe. There were no postoperative complications that could be definitely attributed to the drugs. Lubitz, working at the same clinic, reported 14 more cases, using the same medication. Moro used this combination of scopolamine, ephedrine and morphine in 32 urological cases, and Ostrčil for painless delivery. Similar results with the combination of eucodal, scopolamine and ephedrine in surgical operations have been reported by Dax and Weigand from 145 cases and by Wagner from several hundred cases. Merck has patented the scopolamine-ephedrine combination in England and Austria.

12. In dermatology

a. In urticaria. In view of the fact that ephedrine resembles epinephrine it has been tried out clinically in allergic conditions other than asthma and hay fever. T. G. Miller treated two cases of acute urticaria with ephedrine given by mouth and recorded beneficial

results. Kesten made a careful study with ephedrine in a large series. She found that in 11 cases of chronic urticaria with angioneurotic œdema, 7 were cured, 2 improved and 2 unaffected. Several patients in this group had had urticaria almost continuously for years but became free from symptoms after taking the drug and remained so for some months after the medication had been discontinued. Results are less favorable in cases without œdema. Of 6 patients with chronic urticaria 2 had complete relief, 2 showed improvement and the remaining 2 no change, following the oral use of ephedrine. In 3 cases of papular urticaria, 2 of erythema multiforme and 2 of chronic eczema there was practically no relief except for lessened itching. Similarly, in a case of mild urticaria following the administration of serum but with no other symptoms of serum sickness, ephedrine produced no relief. Althausen and Schumacher reported that ephedrine gave prompt relief from itching and brought about disappearance of the lesions in a case of toxic erythema accompanied by pruritus, and effected improvement in 2 cases of urticaria but gave no relief in 5 other cases of urticaria and 3 cases of angioneurotic œdema. Encouraging results were obtained by Thomas in a few cases, and by Munns and Aldrich in a case of urticaria; by Berger and Ebster in a case and by Wilkinson in 2 cases of chronic urticaria; by McPhedran in a case of angioneurotic œdema; and by Ségard in a case of painful and purulent polymorphous erythema.

b. In dermatitis medicamentosa. Perutz recommends the use of ephedrine in anaphylactic reactions from turpentine. Stokes and McIntyre studied 68 cases which showed reactions towards arsphenamine injections. They found that in 57.5 per cent of them ephedrine relieved such symptoms as nausea, headache, vertigo, dizziness, urticaria, pruritus, pain, choking, coughing and repeated nitritoid crises. Besides, ephedrine reduced the fall of blood pressure from 28 to 6 mm. Hg.

c. In leprosy. The fact that epinephrine relieves the nerve pains of lepers led Muir and Chatterji to use ephedrine for this purpose in 13 cases. They found that ephedrine does not interfere with the simultaneous use of potassium iodide, and its action lasts for 12 to 24 hours. In their opinion, the beneficial effect is probably due to contraction of the arterioles of the nerve trunks, thereby relieving their

vascular engorgement. They admit that in certain cases ephedrine does not give relief. Cochrane and Mittra reported 10 cases of leprosy in which the lepra reactions, such as nerve pain, joint pain, swelling and other manifestations, were controlled by ephedrine. They consider it an extremely useful drug in relieving the distressing symptoms of lepra reactions. The relief is usually complete. Ephedrine has no action on the temperature, nor does it reduce the eruptions which appear during reactions in skin cases. According to these authors, the lepra reactions are allergic manifestations and ephedrine like epinephrine, is able to alleviate allergic conditions.

13. In dysmenorrhea

Assuming that dysmenorrhea is due to local or general increase of parasympathetic activity, Lang used ephedrine in 30 cases of essential dysmenorrhea. There was not only complete freedom from or diminution of pain, but also diminution of menstrual flow by one-half to one-third. Ephedrine was given as soon as pain appeared, usually 2 to 3 times a day. One patient experienced pain and a feeling of cold in the legs. Palpitation and tremor were observed in other cases. In one patient, repeated curettage did not produce any effect, but the use of ephedrine actually yielded good results.

VI. ACTION OF SYNTHETIC EPHEDRINE AND COMPOUNDS OPTICALLY ISOMERIC WITH OR RELATED TO EPHEDRINE

1. Synthetic or dl-ephedrine

No sooner was the natural or *l*-ephedrine introduced to medical use than the synthetic or *dl*-ephedrine became a subject of study. It is optically inactive and is marketed by Merck under the name of *Ephetonin*. Kreitmair showed that qualitatively there is no difference between the action of natural and synthetic ephedrines. Thus, it has a prolonged pressor action, antispasmodic action, detoxifying action against scopolamine or morphine, oxytocic action and effectiveness by mouth. His results are in general confirmed by Chen and by Pak and Read, although the last two authors believe that the synthetic product is less sympathomimetic than the natural. Coelho in chloralosed dogs observed with electrocardiograms the appearance of

extrasystoles, changes in Q.R.S. and alteration in T waves, block, and finally ventricular fibrillation, with various doses of synthetic ephedrine. As with the natural drug, Chen found relaxation of the isolated rabbit's intestine, hyperglycemia in rabbits, mydriatic action in animals and in men, contraction of the nasal mucous membrane and accessory sinuses and a decrease followed by an increase of the kidney volume, with synthetic ephedrine. He also observed that there is a diminution or loss of pressor action if it is injected intravenously after a previous dose of itself or of natural ephedrine.

In men, Hess, Petow and Wittkower, Saxl, Berger, Ebster and Heuer, and Nardelli reported a rise of systolic blood pressure by oral or rectal administration or subcutaneous injection of synthetic ephedrine. Berger, Ebster and Heuer, and Nardelli noted a primary leucopenia and secondary leucocytosis following the subcutaneous injection of synthetic ephedrine. Lublin showed that the synthetic product, when given by mouth, like the natural, produces hyperglycemia and inhibits the conversion of carbohydrates into fat. Cannavò obtained similar results. Euler and Liljestrand showed that synthetic ephedrine in men increases the O_2 consumption and the minute cardiac output. Synthetic ephedrine delays the emptying time of the stomach and decreases the gastric acidity, as reported by Takács. Fonseca and Trincao state that oral administration diminishes but subcutaneous injection increases the gastric acidity.

Quantitatively, Kreitmair in his preliminary communication concluded that there was no difference between the natural and synthetic ephedrines. Hess shared the same opinion for men by oral or rectal administration. Petow and Wittkower, Saxl, and Berger, Ebster and Heuer, on the other hand, seem to agree that synthetic ephedrine has a weaker pressor action in men. Chen in 9 subjects found that the changes in blood pressure by the oral use of synthetic ephedrine are much less uniform than by that of natural ephedrine. Compared indirectly in pithed cats against epinephrine, the average ratio, as found by Chen, of the intensity of pressor action of synthetic ephedrine to that of natural ephedrine with optimal doses is 1:1.33. Curtis, using the same method, determined the ratio to be about 1:2. Schaumann, and Launoy and Nicolle arrived at the same conclusion. Pak and Read, making direct comparisons in anesthetized dogs, gave the

ratio of synthetic to natural ephedrine as 0.7:1 (or 1:1.43), which is close to the one obtained by Chen. A quantitative difference can also be shown in their mydriatic action. Under controlled illumination and with accurate measurements, Chen determined in Caucasians the average ratio of the mydriatic action of synthetic ephedrine to that of natural ephedrine to be 1:1.29. Regarding the toxicity, Kreitmair found it to be the same in mice either by intravenous injection or by oral administration. Chen recorded that synthetic and natural ephedrines, in the form of the hydrochlorides, given intravenously, both have a M.L.D. of 60 mgm. per kilogram in white rabbits. Pak and Read state that synthetic ephedrine is less toxic than natural ephedrine in frogs, rats, rabbits and dogs; the reverse is true for hamsters. King and Pak studied in anesthetized dogs the ratio of the shrinkage of the nasal mucous membrane produced by natural and synthetic ephedrines, respectively, and determined it to be 1:0.8.

Clinically, synthetic ephedrine has been tried wherever natural ephedrine is indicated. Petow and Wittkower treated 20 cases of bronchial asthma by oral use of synthetic ephedrine. Their results showed that in 12 cases the synthetic product rendered daily injections of epinephrine and asthmolysin unnecessary, in 5 it effected transient improvement without preventing severe attacks, but in the remaining three there was no response to the drug. Fischer treated 11 asthmatics with synthetic ephedrine and recorded improvement in 10. Berger and Ebster in an elaborate investigation recorded unquestionable benefit from synthetic ephedrine in 10 cases of asthma and less significant results in 2 severe cases of the same ailment. Neustadt studied 22 cases of bronchial asthma with synthetic ephedrine, and obtained good results in 16. Ségard treated 70 cases of asthma with the same drug and reported relief in 60 per cent, temporary or irregular improvement in 30 per cent, but no effect in 10 per cent. Gay and Herman (cited by Chen) used synthetic ephedrine in 16 cases of bronchial asthma, recorded relief in 7, questionable relief in 1, and no relief in 8. Favorable results in the treatment of asthma with the synthetic compound have also been reported by Jankowski, Beck, Guttmann, and Hemming. The majority of these investigators appear to agree that synthetic ephedrine is useful, like the natural product, in the prevention and arrest of mild and moderate attacks of asthma but less promis-

ing in severe cases, and that it has a weaker action but produces less untoward symptoms than natural ephedrine. The dosage of synthetic ephedrine varies according to individual tolerance, but the average dose lies between 25 and 150 mgm. per os.

Saxl treated 11 cases of emphysema with synthetic ephedrine, and reported success in 8 but no effect in 3. Similar improvement was observed by Berger and Ebster in 3 cases of chronic bronchitis with emphysema, chronic bronchitis and bronchitis associated with pulmonary tuberculosis. In hay fever Berger and Ebster, Kreitmair and Nardelli advocated the oral use and local application of synthetic ephedrine. Berger and Ebster observed relief of headaches in one case of hemicrania with angioneurotic œdema, but no effect in a case of chronic urticaria. Improvement of symptoms was reported by Fränkel in a severe case of urticaria, by Sack in 20 cases of eczema, and by Nardelli in three cases of alimentary urticaria and two cases of arsphenamine intolerance. Michalowsky was successful in relieving malaise from roentgenological treatment, Poppe in controlling the untoward symptoms of withdrawal of morphine in two addicts, and Parade and Voit in arresting the attacks in a single case of Adams-Stokes' syndrome. In practically every instance, synthetic ephedrine was given by mouth. For acute infectious rhinitis, Berger and Ebster used a 5 per cent solution of synthetic ephedrine as a spray. Slack (cited by Chen) found that in 4 cases of hypertrophied turbinates and 3 cases of acute rhinitis, a topical application of the 5 per cent solution produces a marked contraction of the turbinates. In a few other cases of swollen turbinates, where natural and synthetic ephedrine were used side by side in the same individuals, he was unable to detect any significant difference between their constricting power. Fränkel described a case of vasomotor rhinitis in an opera singer, with symptoms of sneezing, running of the eyes and dyspnea which were controlled by the oral administration of synthetic ephedrine. Sattle advocated the use of synthetic ephedrine in ophthalmology. According to him, a solution containing 5 per cent of synthetic ephedrine and 0.3 per cent of homatropine produces good dilatation of the pupil.

2. Pseudoephedrine

The natural pseudoephedrine is dextro-rotatory and is obtained from several species of *Ephedra*, including the ones yielding natural or *l*-

ephedrine. The mydriatic action of pseudoephedrine was first studied by De Vriesse (1889). He observed that a 10 to 12 per cent solution when applied locally to the eye of men produces, in from 30 to 35 minutes, mydriasis which lasts from 6 to 9 hours. There are no secondary effects after a single instillation, nor after its prolonged use, and no changes in intra-ocular pressure. Günsburg (1891) in an extensive study on animals and 120 patients presented evidence that the mydriasis produced by pseudoephedrine is caused by sympathetic stimulation. Grahe (1895) observed a slight rise of blood pressure in curarized cats after subcutaneous injection of the drug, and depression, block, arrhythmia and stoppage of the frog's heart at diastole, following the administration of pseudoephedrine. Fujii (1925) made a comparative investigation of pseudoephedrine with ephedrine. He reported that pseudoephedrine has a weaker pressor action in rabbits and a weaker mydriatic action on the enucleated frog's eye. It dilates the blood vessels in small doses but constricts them in large concentrations, as shown by the perfusion of the frog's legs and the rabbit's ear. Similarly, it relaxes the isolated rabbit's small intestines in small concentrations but stimulates them in strong solutions. It contracts the isolated rabbit's uterus in all concentrations. On the basis of these data, Fujii concluded that pseudoephedrine, like ephedrine, stimulates the sympathetic nerve endings but, unlike ephedrine, acts on smooth muscles directly in small doses. The same view is held by Pak and Read and by Chopra, Dikshit and Pillai. Chen made a similar comparative study, and reported that pseudoephedrine has a weaker pressor action in dogs and in men, and a weaker mydriatic action in men. Vasodilatation in frogs and toads was reported by Loo and Read. Upon perfusion of the toad's heart, pseudoephedrine in the concentration of 1:20,000 causes a decrease in rate but an increase in amplitude. Larger concentrations (1:200) produce cessation of cardiac activity, as shown by these workers. Pak and Read found that ergotoxine does not invert, but cocaine abolishes, the pressor action of pseudoephedrine. Liljestrand observed that pseudoephedrine contracts the isolated guinea pig's uterus and human uterus and that it has a stimulating action on the fundus of the rabbit's urinary bladder but no effect on the trigone.

Quantitatively, Chen, Wu and Henriksen recently compared indi-

rectly in pithed cats the pressor action of pseudoephedrine and ephedrine, and found the average ratio of the intensity to be 1:5.17; that is, ephedrine is about 5 times as strong as pseudoephedrine. Pak and Read, by direct comparison in anesthetized dogs, concluded that ephedrine is twice as strong as pseudoephedrine. Their method is subject to criticism, as shown by Pittenger. King and Pak compared the shrinkage of the nasal mucous membrane in anesthetized dogs with ephedrine and pseudoephedrine and found the ratio to be 1:0.38. The toxicity was compared by Fujii who found that pseudoephedrine is less toxic in frogs but more toxic in mice. In white rabbits the M.L.D. of pseudoephedrine hydrochloride is 75 mgm. and that of ephedrine hydrochloride is 60 mgm. per kilogram of body weight, as shown by Chen, Wu and Henriksen. Pak and Read reported that pseudoephedrine is less toxic than ephedrine in frogs, rats, rabbits and dogs; the reverse is true in hamsters.

Clinically, Howard and Lee tried out a 10 per cent solution of pseudoephedrine in their eye clinic and concluded that it is an uncertain mydriatic and has no place in the treatment and examination of ophthalmic diseases. Since its action is much weaker than that of either natural or synthetic ephedrine, it is not used in this branch of medicine, although it has been advocated by Chopra, Dikshit and Pillai on the basis of their experimental results.

3. Other optical isomers of ephedrine

Kreitmair showed that *d*-ephedrine is weaker in pressor action than *l*-ephedrine. This has been confirmed by Chen, Schaumann, and Launoy and Nicolle. Recently, Chen, Wu and Henriksen compared the pharmacological activity of the six optical isomers of ephedrine, courteously supplied by E. Merck of Darmstadt and Merck and Co., Rahway, N. J. The results are summarized in table 4. It will be seen that the mydriatic action of *l*-ephedrine and *d*-pseudoephedrine is greater than that of *d*-ephedrine and *l*-pseudoephedrine, respectively. When indirectly compared for pressor action in pithed cats with epinephrine, *l*-ephedrine is found to be about 3 times as strong as *d*-ephedrine, and *d*-pseudoephedrine 7 times as strong as *l*-pseudoephedrine. *l*-Ephedrine, the strongest isomer, is 35 times as powerful as *l*-pseudoephedrine, the weakest isomer of the six. When given by

mouth to men in the same quantity, *d*-ephedrine and *l*-pseudoephedrine do not appear to raise the systolic blood pressure while the other four isomers do. Of the two sets of isomers *d*-ephedrine and *l*-pseudoephedrine have the least toxicity.

TABLE 4

Pharmacological activity of the optical isomers of ephedrine

EPHEDRINE ISOMER	MYDRIASIS	RATIO OF PRESSOR ACTION IN ANIMALS	PRESSOR ACTION IN MEN PER OS	M.L.D IN WHITE RABBITS
				mgm. per kgm.
l-	+++++	35.15	+	60
dl-	+++++	26 40	+	60
d-	+++	11 90	−	80
d-Pseudo-	++++	6 80	+	75
dl-Pseudo	+++	4 00	+	70
l-Pseudo	+	1.00	−	80

4. Compounds related to ephedrine

It has been shown that β-phenylethylamine, $C_6H_5 \cdot CH_2 \cdot CH_2 \cdot NH_2$, has a stronger pressor action than ephedrine (Chen, Alles) but is useless when given by mouth. The M.L.D. of the hydrochloride of β-phenylethylamine in white rabbits, given subcutaneously, is 300 mgm. per kilogram of body weight.

Phenylethanolamine, $C_6H_5 \cdot CHOH \cdot CH_2 \cdot NH_2$, was first synthesized by Kolshorn (Ber. deut. chem. Gesell., 1904, xxxvii, 2474), later by Rosenmund (Ber. deut. chem. Gesell., 1913, xlvi, 1034), and Mannich and Thiele (Arch. Pharm., 1915, ccliii, 181), and is covered by two German patents (D. R. P. 193, 631 and D. R. P. 244,321). The pressor action of this compound was described by Barger and Dale (Jour. Phys., 1910–11, xli, 19) and by Hirose. Alles recently found that it has a blood pressure effect in rabbits that is initially greater than and finally comparable with that of ephedrine, and a lower toxicity in guinea pigs by subcutaneous injection. The same author states that its toxicity is higher than that of ephedrine in rabbits by intravenous injection, while Chen, Wu and Henriksen reported the reverse in white rabbits. Tainter believes that the action of phenylethanolamine is on the smooth muscles directly. Miller and Piness showed that this compound does not raise the blood pressure in men

when taken by mouth and is useless in the treatment of asthma, but its activity on the congested nasal mucous membrane is in every respect comparable to that of ephedrine. Their results are in general confirmed by Chen, Wu and Henriksen.

Nor-ephedrine, $C_6H_5 \cdot CHOH \cdot CHCH_3 \cdot NH_2$, was obtained in a racemic form by Rabe and Hallensleben (Ber. deut. chem. Gesell., 1910, xliii, 2622), Calliess, Nagai, and Eberhard (Arch. Pharm., 1917, cclv, 140). Nagai patented his product under the name of *Mydriatine* in the United States (U. S. Pat. 1,356,877) and in Japan (Jap Pat. 27,056). Miura found that this compound (*mydriatine*) has a strong mydriatic action in men. The pupil begins to dilate in 20 to 30 minutes and the mydriasis lasts for 24 to 36 hours. The accommodation is not impaired. Hirose first observed its pressor action in animals. Amatsu and Kubota concluded that its action is quantitatively the same as that of ephedrine. Their data show that the M.L.D of *mydriatine sulphate*, given subcutaneously, is 0.4–0.5 mgm. per gram in frogs, and 400 to 500 mgm. per kilogram in rabbits. Chen, Wu and Henriksen conclude from their study of ephedrine homologs and isomers that primary amines are more powerful than their corresponding methylated derivatives, and predicted that nor-ephedrine would be stronger than *dl*-ephedrine. This has been found to be true. The compound also raises the systolic blood pressure in men when given by mouth in 50 mgm. dosage. Its M.L.D. intravenously in albino rabbits is approximately 70 mgm. per kilogram of body weight. Kanao succeeded in resolving the racemic mixtures of nor-ephedrine into six optical isomers. According to Hirose (cited by Kanao), the order of activity of these optical isomers is as follows:

Nor-*d*-pseudoephedrine > nor-*dl*-ephedrine = nor-*l*-ephedrine
Nor-*d*-ephedrine < nor-*l*-ephedrine
Nor-*d*-pseudoephedrine > nor-*l*-pseudoephedrine < nor-*l*-ephedrine

Nor-*d*-pseudoephedrine also occurs in Ma Huang, as shown by Smith, and confirmed by Nagai and Kanao. Chen, Wu and Henriksen reported that nor-*d*-pseudoephedrine has a weaker action than *l*- or *dl*-ephedrine, but a stronger action than *d*-pseudoephedrine. It raises the systolic blood pressure in men when given by mouth.

Tiffeneau, and Tiffeneau, Lévy and Boyer synthesized three com-

pounds of the general formula $C_6H_5 \cdot CHOH \cdot CHR \cdot NH_2$, where R is ethyl, propyl or phenyl. The ethyl compound, $C_6H_5 \cdot CHOH \cdot CHC_2H_5 \cdot NH_2$, called nor-homoephedrine, has a prolonged pressor action and a M.L.D. of 130 mgm. per kilogram in guinea pigs by subcutaneous injection, and inhibits the movements of the isolated dog's intestines, as shown by Tiffeneau. Its pressor action is weaker than that of ephedrine (Chen, Wu and Henriksen). The propyl and phenyl derivatives have a depressor action, as reported by Tiffeneau, Lévy and Boyer.

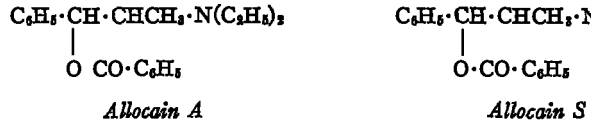
Hyde, Browning and Adams synthesized a series of compounds of the general formula $C_6H_5 \cdot CHOH \cdot CHR' \cdot NHR''$, where R' is hydrogen, methyl, or *n*-propyl, and R'' is methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl or *n*-amyl. Most of these substances, including two prepared by Manske—in which R' is methyl and R'' is oxyethyl or benzyl—were studied pharmacologically and compared with ephedrine by Chen, Wu and Henriksen. They are weaker than ephedrine. The general conclusion drawn by these workers was that with increase in the number of C-atoms in R' and R'' the cardiac depressant action increases, the toxicity rises and the pressor action becomes a depressor action when R' or R'' is equal to a propyl or higher alkyl group.

Kanao prepared a similar series of compounds of the general formula $C_6H_5 \cdot CHOH \cdot CHCH_3 \cdot NHR$, where R is ethyl, *iso*-amyl, heptyl, benzyl, *o*-hydroxybenzyl, *o*-vanillyl, vanillyl, piperonyl, *m,p*-dihydroxybenzyl, furfuryl or citryl. He states that the hydrochloride of the citryl derivative has a strong local anesthetic action.

l-Methylephedrine, a tertiary amine isolated from Ma Huang by Smith, was proved to be much less active than ephedrine, a secondary amine, by Chen, Wu and Henriksen. The same conclusion was reached by Curtis with a series of tertiary amines related to ephedrine of the general formula $C_6H_5 \cdot CHOH \cdot CHCH_3 \cdot NR'R''$, where R' is methyl or ethyl, and R'' is methyl, ethyl, oxyethyl, *n*-propyl, *iso*-propyl or butyl. Some of these compounds, however, produce dilatation of the bronchi equal to that of ephedrine. The tertiary amine of the formula $C_6H_5 \cdot CHOH \cdot CHC_2H_5 \cdot N(C_4H_8)_2$, prepared by Hyde, Browning and Adams, has a depressor action, as shown by Chen, Wu and Henriksen.

Nagai synthesized the following two substances with the idea that

they might possess the anesthetic property of cocaine and the styptic action of epinephrine:



Allocain A *Allocain S*

His process has been patented in Canada (Can. Pat. 177,019), Japan (Jap. Pat. 32,476) and the United States (U. S. Pat. 1,399,312). Kubota studied *allocain S* and found it to have a local anesthetic property but that it produces a primary fall of blood pressure in animals. The substance causes local irritation and necrosis so that its clinical use does not seem justifiable.

Beaufour prepared ω-methoxymethylephedrine, $C_6H_5 \cdot CHOH \cdot CH(CH_2 \cdot OCH_3) \cdot N(CH_3)_2$, and found it to have a local anesthetic action. Brauchli and Cloetta reported that diallylephedrine, $C_6H_5 \cdot CH(OC_3H_5) \cdot CHCH_3 \cdot NCH_3(C_3H_5)$, has a depressor action.

Emde and Runne synthesized α-isoephedrine, $C_6H_5 \cdot CHNHCH_3 \cdot CHOH \cdot CH_3$. This compound is of interest because ephedrine for some time was considered to have the same structural formula.

Dulière made synthetically several ethers of phenylpropanolamine, and studied their pharmacological action.

Tyramine, HO⟨⟩$CH_2 \cdot CH_2 \cdot NH_2$, was proven to have a stronger pressor action than ephedrine but to be useless when given by mouth in men, as shown by Chen and Meek. *Sympatol*, HO⟨⟩$CHOH \cdot CHNHCH_3$, which has recently been studied as a possible substitute for ephedrine by Ehrismann, Lasch, and Ehrismann and Maloff, has, on the other hand, a weaker pressor action than ephedrine, as observed by Chen, Wu and Henriksen. In view of the fact that the presence of an OH group at the *p*-position usually intensifies the action, and the introduction of a methyl group on the α-C-atom from the N-atom prolongs the action, Chen, Wu and Henriksen suggested the synthesis of the compound HO⟨⟩$CHOH \cdot CHCH_3 \cdot NH_2$, which was soon achieved by Hartung of Sharp and Dohme, Baltimore. It has in fact a prolonged and stronger pressor action, and is much less toxic, than either *dl*- or *l*-ephedrine in animals, but it has not been demon-

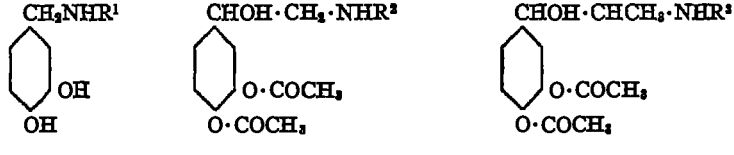
strated that it produces systemic effects when given by mouth in men. Further study is needed here.

Tiffeneau, Lévy and Boyer synthesized *p*-methoxy-norhomoephedrine, CH_3O⟨⟩$CHOH \cdot CHC_2H_5 \cdot NH_2$, and found it to possess a greater pressor action than nor-homoephedrine. Kohler prepared *p*-methoxyephedrine, CH_3O⟨⟩$CHOH \cdot CHCH_3 \cdot NHCH_3$, and *m*-methoxy-*p*-oxyephedrine, HO⟨⟩$CHOH \cdot CHCH_3 \cdot NHCH_3$ (CH_3O), and found them to have no pressor action in rabbits.

It is universally agreed that epinephrine HO⟨⟩$CHOH \cdot CH_2 \cdot NHCH_3$ (HO), has a strong but fleeting action, while ephedrine has a weaker but more prolonged action. The latter produces systemic effects when given by mouth. *o*-Dihydroxyphenylethanolamine, HO⟨⟩$CHOH \cdot CH_2 \cdot NH_2$ (HO), also has a stronger pressor action than ephedrine, as shown by Hirose.

The compound HO⟨⟩$CHOH \cdot CHCH_3 \cdot NH_2$ (HO), is mentioned in the German patent literature (D.R.P. 254,438, 256,750, 269,327) and has been studied pharmacologically by Tiffeneau (1920). The latter found that an *l*-isomer resolved from its racemic mixture has 60 to 75 per cent of the activity of *l*-epinephrine, but he did not study the duration of its action nor its absorption from the gastrointestinal tract. It seems desirable to compare its action with that of ephedrine.

Kanao recently synthesized three series of compounds having the general formulae:



where R^1 is methyl, ethyl or propyl, R^2 is methyl, heptyl, benzyl, piperonyl, diacetoxybenzyl, acetovanillyl or furfuryl and R^3 is methyl,

heptyl, benzyl or diacetoxybenzyl. The physiological activity of these substances has not been reported.

From the above account it appears that there is no difficulty in synthesizing compounds related to ephedrine that are stronger pharmacologically in animals, especially by making primary amines and introducing 1 or 2 OH groups on the benzene ring. A prolonged action may also be imparted to them by introducing a methyl group on the α-C-atom from the N-atom. The absorbability from the gastrointestinal tract seems to be a peculiar feature of ephedrine, and this has made ephedrine particularly useful clinically because the drug can be given by mouth. Among the synthetic compounds, *dl*-ephedrine and *dl*-norephedrine resemble natural ephedrine most closely and deserve a clinical trial. Some other compounds have a strong contracting power on the congested nasal mucous membrane in men, and a comparative study may yield profitable results.

VII. SUMMARY

The following very brief summary is made from the practical point of view.

1. Ephedrine is the chief active principle occurring in the Asiatic species of *Ephedra*. The other constituents that are present in the Chinese species are pseudoephedrine, nor-*d*-pseudoephedrine, *l*-methylephedrine, and *d*-methylpseudoephedrine.

2. Ephedrine is a stable compound. Its solutions are not decomposed on exposure to air, light or heat, or by long standing.

3. Ephedrine has been successfully synthesized by various methods.

4. In mammals, ephedrine in suitable doses raises the blood pressure, increases cardiac activity, dilates the pupil, relieves broncho-spasm, contracts the uterus, more frequently inhibits than stimulates the gastrointestinal tract. These effects can be explained by the stimulation of the myoneural junctions of the sympathetic fibers. In certain instances, there is an additional stimulation of the ganglia. It has been claimed by some investigators that it acts on the smooth muscles.

5. In animals, ephedrine does not have a marked effect on any of the body secretions.

6. There is an increase in the formed elements of the blood and hyperglycemia, following the administration of a suitable quantity of ephedrine.

7. Ephedrine increases slightly the basal metabolic rate and the oxygen consumption.

8. Ephedrine may stimulate the central nervous system.

9. Ephedrine is easily absorbed and has a low toxicity.

10. In clinical use, ephedrine can be applied locally and given by mouth or by injection. Individuals who do not have a vago-sympathetic equilibrium may experience untoward symptoms.

11. Ephedrine has been used with success in the treatment of bronchial asthma, hay fever, whooping cough, bronchitis, postural hypotension and Adams-Stokes' syndrome, in combating the fall of blood pressure in spinal anesthesia, in antagonizing the action of narcotic drugs, in shrinking the congested nasal mucous membrane, and in dilating the pupil for ophthalmic examination. Its value in dermatology, shock and dysmenorrhea is promising.

12. Compared with epinephrine, ephedrine has a less intense but more prolonged action.

13. Of the many synthetic compounds, *dl*-ephedrine and *dl*-norephedrine deserve more extensive clinical trials.

This review is intended to be as concise as possible. Naturally the authors could not discuss many valuable papers as fully as they desired. The literature consists of all those articles available on or before November 1, 1929.

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INDEX

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