

foreigners, in seven the infection was that of a malignant tertian fever. In our limited experience at the Eden Hospital and at a maternity and child welfare clinic run by a missionary society in Calcutta, the incidence of kala-azar during pregnancy is infrequent. In one year in a series of 1,940 cases, the sera of only 17 patients running a temperature were returned as positive to the aldehyde and urea stibamine tests. In addition to these, in 32 cases where the clinical picture was one of kala-azar, urea stibamine was tried empirically with very good results. In our hands quinine has not yet interrupted the course of pregnancy in patients where the malarial parasite has been found in the blood and where the patient has been given alkalis along with the quinine. We never use quinine intravenously but only by the oral or intramuscular route. We tried atabrin in three cases of benign tertian infection with encouraging results and we did not meet with any discoloration of the skin. We have not used plasmochin.

Intestinal parasites are very often responsible for the febrile condition during pregnancy. Gurkha women and people from the Northern parts of the adjoining areas of Bihar and the United Provinces suffer from heavy helminthic infections.

Intra-uterine death of the foetus occasionally is the cause of a rise in the temperature. In the early months of gestation the ovum may separate from the wall of the uterus, totally or partially. If it is not expelled it remains in the uterus as a carneous mole. The rise in the temperature may be due to the absorption of fibrin from the intra-uterine extravasated blood. In the later months when interruption in gestation occurs, disintegration of the foetus, the placenta and the membranes takes place and absorption of these products possibly reacts on the mother, producing 'fever'. Beyond the rise in temperature and a feeling of malaise there may not be any definite indication pointing to the death of the foetus. If the symptoms are not urgent, it is safe to wait for a fortnight, or if possible for a month and, at the end of the period, examine the uterus to find out if it has enlarged in size. If the uterus remains stationary or retrogresses, suspicion as to the death of the foetus is confirmed. In more advanced pregnancies absence of foetal heart sounds and foetal movements, where there were such sounds and movements previously, clinches the diagnosis at once. X-rays help the diagnosis in advanced cases. A flattened and deformed calvarium, a hyperflexed or super-extended spine, and irregularly placed limb bones all point to the fact that the foetus is dead and the skeleton is in the process of intra-uterine maceration. It is easy to empty the uterus of the products of conception in the later months, but in the early months it is not always

(Continued at foot of next column)

TOXIC EFFECTS OF EPHEDRINE—A WARNING

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THE alkaloid ephedrine is obtained from several species of ephedra growing in China and India. Under the name of *Ma Huang* this herb has been in use in the Chinese indigenous medicine for about 5,000 years. The development of a useful modern drug out of this ancient remedy is due to the pioneer work of a Japanese chemist, Nagai (1887), who isolated this alkaloid in a pure form and two Japanese physiologists, Amatsu and Kubota (1917), who demonstrated the essentially sympathomimetic (epinephrine-like) effects produced by ephedrine. Chen and Schmidt (1924) reopened the therapeutic possibilities of the drug by conducting a series of careful studies with regard to its physiological properties. Chopra and his collaborators (1929, 1930, 1931) did a large amount of work on the Indian species of ephedra and worked out many points in connection with the pharmacological action and therapeutic properties of not only ephedrine but the allied alkaloid, pseudo-ephedrine.

The result of all this work has been that during the last ten years ephedrine has risen from obscurity to a widespread popularity among medical men in all parts of the world.

(Continued from previous column)

so easy. The placenta is in most cases adherent and does not separate easily. We use and recommend the very safe and simple technique of introducing laminaria tents into the uterus along with the injection of glycerine and tincture of iodine into the uterine cavity. This operation is carried out as follows:—The patient is in the lithotomy position; no anaesthetic need be used. Two or three laminaria tents are introduced into the uterine cavity the first day, and after twenty-four hours these are removed, a thick india-rubber catheter (no. 12 Jacques) is introduced into the uterine cavity through which pure sterile glycerine and tincture of iodine (seven drachms of glycerine and one drachm of iodine) is injected into the uterus. At the same sitting three or more fresh tents are introduced. The uterus usually empties itself completely after this but occasionally four half-hourly injections of 0.25 c.cm. of pituitrin may be necessary.

The above observations have been made under the guidance of Lieut.-Colonel V. B. Green-Armytage, M.D., F.R.C.P., F.C.O.G., to whom I am grateful for allowing me to use the records of the Eden Hospital and to publish records of some of his patients.

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Its range of utility is so wide that there is hardly a medical practitioner who has not had occasion to use the drug some time or other in the course of his professional career. The therapeutic claims made for the drug were examined by the Council of Pharmacy and Chemistry of the American Medical Association in 1926 and they were so struck by the potency and usefulness of the alkaloid that it was at once introduced into the United States Pharmacopœia. The new sixth edition of the British Pharmacopœia published in 1932 has also recognized it and it has now become an established remedy.

At the present time this alkaloid is widely used for a variety of conditions and the literature is full of many interesting and instructive articles regarding its pharmacological action and therapeutic uses. It has been used with success in the treatment of bronchial asthma, hay fever, whooping cough, bronchitis, postural hypotension and Stokes-Adam's syndrome. It has been employed in combating the fall of blood pressure in spinal anaesthesia, in antagonizing the action of narcotic drugs, in shrinking the congested nasal mucous membrane, and in dilating the pupil for ophthalmic examinations. Its effects in allergic dermatitis, shock and dysmenorrhœa are promising. Of all the diseases for which the drug has been tried, asthma is the commonest condition. The fact that it can be effectively given by the mouth and that its action is more lasting than epinephrine has made it a very popular remedy. Its reputation as an efficient anti-asthmatic has spread even amongst laymen and in many cases the drug is taken on a patient's own initiative without his consulting a physician.

From time to time attention has been called to certain untoward effects from the use of this drug whether given by the mouth or by injection. Miller (1925) by using doses of 50 to 125 mgm. (0.75 to 1.87 grains) found no definitely harmful effects but recorded that a few patients complained of palpitation, nervousness and nausea. One who had marked myocardial degeneration showed a transient pulsus alternans one hour after the drug was administered. Production of nausea after administration of the drug in cases of asthma and hay fever was reported by Althausen and Schumacher (1927). Anderson and Homan (1927) used ephedrine in whooping cough in children. Though the drug was efficacious in preventing the spasmodic attacks, they observed in several cases marked restlessness, sweating, abdominal pain, discomfort, and apparent suppression of urine. That these symptoms were produced by ephedrine is shown by the fact that they disappeared when the drug was discontinued and reappeared when it was resumed. Middleton and Chen (1927) in a series of 41 patients found that palpitation of the heart was the prominent feature when the dose of ephedrine was larger

than 80 mgm. (1½ grains); vomiting, dizziness, nervousness, headache and insomnia were also observed in several cases. Tremors, weakness, sweating, and sometimes a feeling of warmth all over the body were also noted. These symptoms usually abated shortly after the blood pressure began to fall; this fall occurs in one to seven hours after administration. Four out of eleven cases in this series showed extrasystoles of ventricular and auricular origin after ephedrine which could be demonstrated with the electro-cardiograph. Another patient developed paroxysms of tachycardia which lasted for a few minutes at a time and then stopped. Bloedorn and Dickens (1928) described a case of cardiac asthma in which cardiac embarrassment, including pulsus alternans, marked tachycardia and cardiac decompensation occurred after administration of ephedrine. Pennetti (1928) observed, by means of electrocardiography, that ephedrine increased the frequency of pre-existing extrasystoles in two cases but produced no change in a case of auriculo-ventricular block of vagal origin. Chopra and his co-workers (1929) first pointed out in this country the dangers which may attend the indiscriminate use of this alkaloid. During recent years a number of cases have come to our notice which leave little room for doubt that the serious effects of the alkaloid have not been fully appreciated by the medical profession in this country. An analysis of the history sheets of a large number of patients in our asthma clinic revealed the frequency with which certain unpleasant side-effects were produced following the administration of ephedrine. We have therefore thought it necessary to give the results of our experience and sound a note of warning regarding its indiscriminate use.

TOXIC EFFECTS

Acute onset.—The most usually noted unfavourable symptoms in our series have been those referable to the *cardiovascular system*. Acute precordial pain resembling an attack of angina with palpitation and profuse sweating, particularly on the forehead, has been found quite commonly. In many persons these symptoms are not acute enough to be particularly noticed or to call for any immediate attention or interference. Tremors of the extremities, a feeling of warmth, flushing all over the body and a dull throbbing sensation in the region of the temples have not uncommonly been complained of by the patients. Faintness, loss of muscular tone and disinclination to physical exertion were observed in two patients. Other symptoms were irregular and rapid pulse, widely dilated pupils, feeble heart beats, and dyspnoic type of respiration. In fair patients, a distinct flush in the malar regions and over the ears may be noticeable.

Disagreeable symptoms in connection with the *gastro-intestinal tract* are less commonly met

with. Nausea, vomiting and colic have been complained of by at least four individuals in our series. Both vomiting and nausea become more intense if the drug is given after a heavy meal. Nausea is sometimes intractable and continues for 24 to 36 hours, but generally disappears within 8 to 10 hours after the drug is stopped. Abdominal distress and a peculiar vague feeling of discomfort round the umbilicus were complained of by two patients. Loss of appetite is not infrequently produced. Constipation with associated flatulence and distension has been a common complaint in those taking the drug for prolonged periods.

Affections of the *genito-urinary system* are observed in the form of dysuria, anuria, and spermatorrhœa. One patient reported complete retention of urine for 24 hours after the administration of ephedrine (4 tablets in the course of 24 hours). No reliance was placed on his version but the presence of a fully distended bladder left no room for doubt. Application of heat and a gentle pressure from above helped him to pass large quantities of pale yellow urine easily. No reason for the retention of urine other than the use of ephedrine could be found in this case, and our opinion was corroborated by the fact that the condition recurred three days later when the drug was again taken and again disappeared when it was discontinued. Dysuria has been the prominent symptom in several patients. In one of these, albumin could be detected on examination of urine. There may be complete relaxation of the bladder sphincter resulting in involuntary micturition in some cases. Spermatorrhœa was complained of by two patients; one of them, a chronic asthmatic aged 46 years, refused to take the drug as it always induced a watery discharge from his urethra. Curiously enough, increase of sexual power has been reported by another who came back for the drug more for the aphrodisiac effects which he experienced than for the relief of asthma.

Many of the untoward effects referred to above have been noticed to occur in groups in the same individual. Thus, patients showing circulatory reactions usually complained of precordial pain, sweating, palpitation, flushing and tingling sensations simultaneously; very seldom has a single symptom been complained of. The effects become apparent within half an hour after administration of a dose and in the majority of individuals they pass away within 2 to 7 hours. Plethoric patients with systolic pressures above 120 to 130 mm. Hg. are more prone to get these side-effects.

In our series of patients we found that the toxic symptoms usually appeared in those who were having large and frequent doses of the drug. Doses below two grains daily rarely produced any symptoms except in sensitive individuals. No definite statement however can be made with regard to the relationship between

the dose and the appearance of the side-effects. The same dose may produce desirable and remarkably good effects in one patient but may produce equally beneficial results with some discomfort in another and may usher in a train of most undesirable symptoms in a third. According to Pollak and Robitschek (1926) and Gaarde and Maytum (1927) the development of these uncommon signs and symptoms does not depend so much upon the dosage but upon the stability of the nervous system of the individual taking the drug. We have at least two cases in our series in which we can definitely associate the appearance of these symptoms with a neurotic or a neuropathic tendency. Severe headache, faintness and a feeling of numbness in the extremities followed within twelve to fifteen minutes of administration of a half-grain tablet of ephedrine sulphate in one of these patients. Such cases fortunately are rare.

Ephedrine is considered to be a sovereign remedy against asthma and it is used more indiscriminately in this than in any other condition. Many of these cases are not true bronchial asthma and it is not unusual to find cases with involvement of the cardiovascular system being treated with ephedrine. If some of the toxic manifestations referred to above occur in cardiac cases, results may be dangerous. The following two cases are given by way of illustration:—

Case 1.—An Anglo-Indian working girl, aged 24, presented herself at the out-patient department of the School of Tropical Medicine, Calcutta, complaining of shortness of breath, cough, palpitation and a sinking feeling in the chest. She was diagnosed as a case of asthma by a private practitioner and was recommended an antispasmodic mixture and ephedrine hydrochloride tablets (gr. i each) at bed time or with the onset of an attack. The first night after only one tablet the patient felt fairly comfortable and slept well without any cough or paroxysm. The next day she had a busy day in the office and had to exert herself a little more than usual. That night there was a feeling of oppression in the chest, and palpitation and cough returned with increased intensity. She took three tablets of ephedrine one after the other. Within fifteen minutes she felt a sensation of giddiness and a sinking feeling; the precordial pain became intense and she felt that she was going to die. She was put to bed immediately, an ice bag was applied to the head and medical aid was sought. The patient however felt better by the time the doctor arrived but the pain in the chest remained in spite of the stimulants that were administered. Next morning as the asthmatic paroxysm persisted the patient took two more tablets without consulting the doctor, and the symptoms recurred with greater intensity. On examination she was found pale and cyanotic with dark rings round her eyes. She was using the accessory respiratory muscles when she talked and there was an anxious expression in her face. The tonsils were enlarged and slightly congested; râles were heard at the bases of both the lungs. The heart was definitely dilated with a rapid weak beat and a systolic bruit was audible at the mitral area. Systolic blood pressure was 120 mm. Hg. and diastolic 110 mm. Hg. Albumin and hyaline casts were found in the urine.

She gave a history of having rheumatic fever six years ago and another attack two years back. A diagnosis of asthma probably of cardiac origin was made and the patient was admitted into the Carmichael Hospital for

Tropical Diseases. In the hospital, she was more thoroughly examined and the symptoms definitely attributed to heart failure. There was nothing to show that she was suffering from bronchial asthma. Ephedrine was tried in small doses and was found to aggravate the symptoms of cardiac failure and produced the symptoms above described. She was put on absolute rest in bed and digitalis, and the symptoms disappeared in the course of a fortnight.

Case 2.—A Hindu lady, aged 50, had been suffering from asthma for the last six years. She was treated outside with antispasmodics, vaccines, sodium, adrenalin, nasal cauterisation, etc., without relief. She has taken ephedrine times without number for relief of paroxysms and always keeps a bottle by her for use in case of emergency. During the last attack for which she came under observation, she gave a history of having taken four ephedrine tablets within 1½ hours. Immediately there was a sensation of discomfort, precordial pain and distress which became unbearable. There was a hot flush all over the body and the abdomen was distended; flatulence, nausea and palpitation were very distressing. The patient also had intense headache and pain in the eyeballs.

Physical examination revealed a definitely dilated heart and thickened arteries, the chest was emphysematous (barrel-shaped) with sunken lower intercostals. The pulse rate was 100 per minute and there was evidence of missing beats. The blood pressure was rather high (155 mm. Hg. systolic and 130 mm. of Hg. diastolic) indicating hypertension. Albumin and granular casts were detected in the urine.

Ephedrine was discontinued and there was no recurrence of the symptoms. The patient was put to bed and kept under alkalies and digitalis and made a good recovery.

Chronic poisoning.—Prolonged use of ephedrine in therapeutic doses does not usually produce cumulative toxic effects. Individuals who suffer from paroxysms of asthma every night are enabled to remain free from attacks for long periods by taking this alkaloid in doses up to one grain once, twice or even three times every 24 hours. They can attend to their daily work and pass comfortable nights without any permanent ill-effects on the system. Experimental results also appear to bear out these observations. Middleton and Chen (1927) reported a case that received a total quantity of ten grains of ephedrine sulphate in a period of eleven days but showed no untoward effects. Wu and Read (1927) mentioned a case in which ephedrine therapy was continued for three years and caused no ill-effects. Chronic ephedrine poisoning however occurs though it is a much rarer condition. A pale, sallow and cyanosed appearance associated with a mild degree of anemia has been frequently noticed in individuals who are in the habit of taking ephedrine for prolonged periods. Whether this is due to any toxic action of the drug or a natural sequence of the disease itself cannot be definitely stated without a thorough investigation on this point being made.

Habit formation is another undesirable result though it is debatable whether this ever occurs. It is common knowledge that gradually increasing doses are required by patients with chronic asthma for the relief of their attacks. This indicates increased tolerance if not actual habit

formation. In several of our patients we have noticed a peculiar sensation of euphoria produced by the drug. Withdrawal in those cases gives rise to a very uncomfortable feeling and the patients urgently demand to be allowed to resume the drug. Extreme nervousness and insomnia are also frequently met with. There was definitely some craving, though it was certainly not so intense as that felt after narcotic drugs. Whether this craving for the drug is a danger-signal of the early manifestation of a drug habit, or is due to the eagerness of the patients to ward off an impending attack it is very difficult to say. This observation is not in accord with that of Middleton and Chen (1927) and Thomas (1926) who believe that ephedrine is not a habit-forming drug. Higgins (1929) reported a case of chronic ephedrine poisoning which simulated hyperthyroidism in all its essential features, but we have not come across any case similar to the one described by him.

Discussion and comments

There is ample evidence to show both from a study of our own cases and from those recorded by other investigators that toxic manifestations and undesirable side-effects are not uncommonly met with after the use of ephedrine in asthma and other conditions. Some of the subjective symptoms are easily explained when one considers the physiological action the alkaloid produces on the system. Ephedrine in doses of 1 to 10 mgm. per kilogramme is known to cause a rise in blood pressure of anesthetized dogs by 100 or more millimetres of mercury and it is maintained at this level for at least 15 to 25 minutes. In human beings, the rise in pressure is not so high as in animals but it varies from 20 to 65 mm. Hg. It is therefore easy to see that circulatory reactions like palpitation and anginal pain will be produced by the drug, particularly when the systolic pressure is at its highest level. The symptoms are also found to disappear as the pressure returns to normal. Insomnia and tremors are possibly due to stimulation of the central nervous system. Constipation, nausea and anorexia may be explained by the paralytic condition of the gut due to sympathetic stimulation and loss of tone. Headache and throbbing sensations in the temples may be attributed to changes in pressure in the arterioles or veins within the skull.

There is no agreement regarding the dosage required to produce these effects. Ephedrine is undoubtedly not a very toxic alkaloid and consequently there is a wide margin of safety. Its minimum lethal dose when given intravenously in dogs was found by Chen to be from 70 to 75 mgm. per kilogramme body weight. From this it can be inferred that a man weighing 50 to 60 kilogrammes would require about 4 to 5 grammes of the alkaloid to produce a fatal result. In contrast to this the usual therapeutic dose is from ½ to 2 grains (65 to 130 mgms.)

and 7 grains (0.45 gramme) have been given in a single dose without untoward effects. The only explanation of the toxic effects appears to be a state of hypersensitiveness of certain individuals to the drug. Ephedrine is a sympathomimetic drug and stimulation of the sympathetic system in a highly-strung individual may lead to symptoms of sympatho-parasympathetic imbalance. It is also well known that slight differences in the amount of calcium in the blood make the autonomic system very sensitive to sympathomimetic drugs of which ephedrine is one.

Cautions and contra-indications

It should not be forgotten that ephedrine administration sometimes gives rise to unpleasant and dangerous side-effects. The commonest effects are attributable to its stimulant action on the circulation. All cases of asthma should therefore be thoroughly examined with regard to their heart condition before the drug is administered. Great caution should be exercised in using the drug in cardiac disorders especially when there are signs of failing compensation. In angina pectoris the drug is very dangerous. In chronic asthmatics with emphysema and arterial hypertension, ephedrine should not be prescribed.

Individual sensitiveness plays a great part in the production of the unfavourable symptoms. A small dose for one individual may be a large one for another. When in doubt the best plan is to test the sensitiveness of the patient with small doses, say 10 mgm., and establish the maximum tolerated dose. It is only by experience and judgment that these side-reactions can be reduced to a minimum. According to the experience of early investigators, a single dose of 50 to 100 mgm. for an average adult may be given with safety. Hess advocates the use of 1 to 2 mgm. per kilogramme of body weight, but this dose appears to be somewhat large for ambulatory patients. Our own experience indicates that in uncomplicated cases 25 to 30 mgm. ($\frac{1}{2}$ grain) is sufficient to relieve the paroxysm if the drug is going to act at all and if necessary the dose may be repeated two or three times during 24 hours. In complicated cases with secondary bronchial infections, a slightly larger dose may be necessary, i.e., from 60 to 75 mgm. (1 to $1\frac{1}{2}$ grains), and it is not advisable to overstep these limits. In cases which are not of an allergic nature and which are suffering from secondary bacterial infections and other complications such as emphysema, myocarditis, hypertension, albuminuria, etc., ephedrine, though helpful, does not relieve the condition satisfactorily, and it is no good increasing the dose in the hope of getting better results. Arteriosclerotic changes and permanent hypertension have been experimentally produced in rabbits by repeated injections of adrenalin over prolonged periods. Ephedrine

is a sympathomimetic drug belonging to the same class and has a very similar physiological action. When prescribing the drug to patients for indefinite and prolonged periods this should be borne in mind.

Summary

1. Ephedrine is a powerful drug and should be used with caution.
2. The toxic symptoms met with in patients in the authors' experiences have been described in detail.
3. In patients with high blood pressure, cardiac damage and history of anginal attacks ephedrine should not be given. In diagnosing cases of asthma, great care should be taken in separating cardiac asthmas from bronchial asthmas.
4. Ephedrine is quite effective in doses of $\frac{1}{2}$ to 1 grain (30 to 60 mgms.). In adults this dose can be repeated. The cases not relieved by such doses are not suitable for ephedrine treatment.
5. If during the administration of ephedrine, the patient exhibits any toxic symptoms such as palpitation, tachycardia, arrhythmia and vasomotor disturbances, the drug should be discontinued at once. Indiscriminate use of the drug may lead to serious results.

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