Current Practice

TO-DAY'S DRUGS

Methisazone

This drug is marketed by Burroughs Wellcome & Co. under the trade name of Marboran.

Chemistry

Methisazone is N-methyl-isatin β-thiosemicarbazone. This is one of a series of isatin β-thiosemicarbazones which have been shown in the laboratory to have antiviral activity against vaccinia[1] and variola[2] viruses.

Pharmacology

The mode of action is at present unknown. There is evidence that the compound acts specifically to prevent the synthesis of new virus particles and not through the depression of normal cellular metabolism.[3] Cell cultures treated with methisazone will still support the growth of viruses other than vaccinia.[3] The virus of mousepox (infectious ectromelia), which is very closely related to vaccinia and variola, will grow unchecked in mice treated with methisazone at dose levels which completely suppress growth of vaccinia.[4] On the other hand, certain other derivatives of isatin β-thiosemicarbazone will protect mice against ectromelia virus and not against vaccinia.[4]

Clinical Uses

Methisazone breaks new ground in the rational therapy of virus infections. However, it is subject to the limitation that must affect the use of any compound which suppresses viral multiplication. In most virus infections the main period of viral multiplication precedes the onset of symptoms, and an antiviral compound is therefore more likely to be successful as a prophylactic measure than in the treatment of established disease.

Methisazone has proved remarkably successful in the prophylaxis of smallpox. In a recent study in Madras[5] 1,100 people who had been in contact with smallpox infection were given oral doses of methisazone. Only three of them developed smallpox and these were only mild attacks. A control group of 1,126 smallpox contacts were vaccinated but were not given methisazone. In this group 78 people developed smallpox and 12 of them died. Similar trials are now under way in other areas of the world, but their results are not yet available. On the basis of present information, methisazone appears to be remarkably effective in protecting smallpox contacts, and is a particularly valuable addition to the clinical armoury, since vaccination after contact is often ineffective. For long-term protection against smallpox vaccination remains supreme.

Vaccination itself is liable to occasional complications. One of these, the continuing local spread of vaccinial lesions (progressive vaccinia) may be very hard to control, and in a number of such cases methisazone has been used in order to halt the process by preventing further virus multiplication. Experience here is fragmentary. Some cases have undoubtedly cleared up; in others the results have been disappointing. In view of the varied circumstances and programmes of treatment, it is not yet possible to make a critical assessment. In particular the optimum dose for this condition may not have been attained in every case. However, it is certain that methisazone will continue to be used in the treatment of vaccinial complications and its value in such conditions should soon be clarified.

Dosage

The present recommendations are that adults should receive 6 g. methisazone (four capsules of Marboran) a day, taken 3 g. in the morning and 3 g. in the evening. Dosage is halved for children between 3 and 10 and proportionately reduced still further for infants.

Side-effects

The only troublesome side-effects so far noticed have been nausea and vomiting in a proportion of the recipients.

REFERENCES

1 Bauer, D. J., and Sadler, P. W., *Brit. J. Pharmacol.*, 1960, **15**, 101.
2 —— Dumbell, K. R., Fox-Hulme, P., and Sadler, P. W., *Bull. Wld Hlth Org.*, 1962, **26**, 727.
3 Sheffield, F. W., *Brit. J. exp. Path.*, 1962, **43**, 59.
4 Bauer, D. J., ibid., 1963, **44**, 233.
5 —— St. Vincent, L., Kempe, C. H., and Downie, A. W., *Lancet*, 1963, **2**, 494.

Correction. In the article on pronethalol (29 August, p. 555), in the paragraph headed "Indications for Use" the words "ventricular fibrillation" should have read "auricular fibrillation".

ANY QUESTIONS?

We publish below a selection of questions and answers of general interest.

T.A.B. for European Travel

Q.—*Is it advisable for travellers to the south of Spain to be immunized against typhoid and paratyphoid despite the fact that the Spanish tourist office considers that the piped water there is perfectly safe? There have, I believe, been some cases of typhoid in Spain earlier this year.*

A.—It is advisable for travellers to any part of Europe to be immunized against typhoid and paratyphoid whatever tourist offices say.

Travel Sickness in Pregnancy

Q.—*Is there a travel-sickness pill that can safely be taken in early pregnancy?*

A.—There does not seem to be unequivocal evidence that any particular drug is completely safe in early pregnancy. Hyoscine appears to have come under least suspicion, and would probably be the wisest choice if it was essential to use a drug at all.

Prophylaxis for East Africa

Q.—*I have a patient who is visiting Uganda and Kenya for three months. What immunizations are advisable and should prophylactic antimalarial drugs be taken?*

A.—Vaccination against smallpox and yellow fever are required by law of those entering Kenya and vaccination against enteric fever, though not legally required, is

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advisable. In addition, it is a good plan for those who are under the age of 40 to be vaccinated against poliomyelitis and for those of all ages to be inoculated against tetanus.

For prophylaxis in malaria the choice lies between proguanil in doses of 100 mg. daily from the day of entering the malarial area and continued for a fortnight after leaving it; chloroquine 300 mg. (base) weekly or 150 mg. (base) twice weekly; pyrimethamine 25 mg. weekly; or amodiaquine 400 mg. weekly for similar periods.

Salt in Hot Climates

Q.—*Is it advisable to take tablets of sodium chloride when visiting countries with a hot, humid climate causing excessive perspiration?*

A.—Provided one lives a normal life and eats a standard European diet there is no necessity whatsoever to take extra salt as a routine in hot, humid climates. After very heavy exercise, however, where there has been a considerable sweat loss, taking a little extra salt may be a precaution against the development of heat cramps during the subsequent replacement of water, particularly in persons who have not had an opportunity to become properly acclimatized. It should be remembered that most people have an intake of at least 10 g. of sodium chloride per day from all sources and to lose this amount of salt a man would have to sweat about 4 litres or have a weight loss of nearly 10 lb. (4.5 kg.). Some potassium is also lost in the sweat, but this again is readily replaced by a normal diet.

On no account should extra salt be taken when the water intake is limited.

Otitis Media and Flying

Q.—*Is flying contraindicated in patients suffering from chronic otitis media?*

A.—No. The main contraindications to flying with ear disease are whenever a patient is in the acute stage of an upper respiratory tract infection (i.e., a cold) or very soon after an operation for deafness such as stapedectomy. The pressure changes when flying in a properly pressurized aircraft are gradual enough to enable the ear to adjust except when the Eustachian tube is not functioning properly, such as with a head cold, and when sudden pressure changes might disturb a recent ear operation such as in stapedectomy. With chronic otitis media there is usually a perforation in the ear drum and no problem arises.

Wasp Repellents

Q.—*Is there any application which will act as a wasp repellent?*

A.—No substance is known to be specifically repellent against wasps. On the other hand, the best modern repellents, such as dimethyl phthalate (D.M.P.) or diethyl toluamide, repel a wide range of arthropods, and would no doubt be effective against wasps. D.M.P., which has been well known for some years, is widely available. Diethyl toluamide, which is rather better, is made in America and less easy to obtain in Britain.

It should be emphasized that these repellents act by contact; that is to say, they drive away insects which alight on treated skin, but have little or no action at a distance. All exposed skin should be treated, therefore, for complete protection. Treatment is simply by smearing a small quantity over the skin by hand. Undiluted repellent can be used and is most effective, but various preparations are available which may be cosmetically more acceptable. Though toxic when swallowed, the repellents are safe to apply to the skin. On tender areas (such as eyelids and mucous membranes) they may cause temporary smarting. They are solvents for many types of plastic, including rayon, but do not harm nylon, wool, or cotton fabric.

Seasickness

Q.—*Why do some people get seasick and not others?*

A.—There is no simple answer, but it is known that seasickness and other forms of travel sickness do not depend on any physiological or psychological characteristics. Infants are less likely to be seasick than others, perhaps because the reflex pathways are not well developed. Susceptibility later declines with age, perhaps because general responsiveness diminishes, or because of adaptation through more experience of wave motion.[1]

If movements are severe enough everybody can be made sick. This may mean that the reflex is present in all, but that the level of responsiveness differs. In the higher animals the level of reflexes is largely controlled by the brain, and habituation is the main process whereby responses to repeated stimuli can be reduced or abolished. Habituation could sometimes inhibit the reflex of vomiting before the stimulus of wave motion has continued long enough to produce a response. But if a person has been seasick before the reflex of vomiting and the sensations of seasickness may be reinforced by conditioning stimuli, such as the smell of a ship or the swaying of a curtain. Indeed it is within the bounds of possibility that the interplay of habituation and conditioning may determine susceptibility to seasickness.[2]

REFERENCES

1 Chinn, H. I., and Smith, P. K., *Pharmacol. Rev.*, 1955, 7, 33.
2 Glaser, E. M., *Proc. roy. Soc. Med.*, 1959, 52, 965.

Notes and Comments

Portable Electrocardiograph.—Dr. W. F. WHEELER (Tuberculosis Dispensary, The London Chest Hospital, E.2) writes: I have been closely associated with the design of several small portable electrocardiographs in recent years, and can assure your expert who answered this question ("Any Questions?" 8 August, p. 359) that his assertion that small machines do not meet his rather poor specifications is incorrect.

With modern techniques, size bears no relationship to performance provided that the design is good, and while, as in any field, there are good and bad units it is obviously foolish to condemn all small electrocardiographs out of hand.

In electronics the trend is to miniaturization, and smaller units than those now available can be expected. The limiting factor is the size of the paper, which, incidentally, I would suggest should not be less than 4 cm. wide.

OUR EXPERT replies: No one who has had to carry an electrocardiograph or who is interested in instruments can fail to welcome the continuing trend to miniaturization and future machines are going to be better technically as well as smaller. The specification quoted in the answer to the question was the minimum acceptable: it was not an optimum specification. It is intended to be met by production machines and to be met throughout the working life of a machine subjected to ordinary use.

Testing shows that the frequency response claimed for some of the smallest machines is simply not met by production machines, and it deteriorates still further during the life of the instrument. In my experience, this has not resulted in the loss of diagnostic information in the electrocardiogram, but it is obvious from inspection of the tracings and does result in loss of confidence in the machine.

It is quite true that the newest of the very small instruments have a much better frequency response and that the frequency response of production instruments approximates to the maker's claims. The owner of such a machine may find himself in the forefront of progress. In my opinion, however, the medium-sized machines (though not all of them) are likely to be a better choice for the general practitioner. The long-term performance, robustness, reliability, and ease of handling of these instruments are better established.

Restless Leg Syndrome.—Mr. W. H. GERVIS (Tunbridge Wells) writes: I was interested in your expert's excellent description of these symptoms ("Any Questions?" 25 July, p. 239), but disappointed in the treatment. The latter mentioned many and varied drugs with long names, but no definite indication as to what they are meant to achieve.

Surely before treating any condition, even if it has been labelled a syndrome, we want to have some idea of what we are trying to treat. Symptoms are apt to develop after sitting, as your expert described; one might add especially after a prolonged period on an ill-designed seat such as a railway carriage. The discomfort can be relieved in such cases by a simple procedure. Roll up a raincoat or the like into a firm cushion, place it behind the lumbar region, then relax with this cushion maintaining a lumbar lordosis. The fact that this affords relief suggests that the symptoms are a referred pain from an imperfect back.

The most common imperfection in this civilized life is disk degeneration. It has been suggested[1] that disks degenerate because we spend most of our lives in a semi-flexed posture, and never stretch and extend fully, as all animals do, to maintain elasticity of disks. Therefore, the patient who is prone to develop this discomfort in his legs in bed should be instructed to practise a full extension of his spine night and morning. This must be done properly, lying on his back, then arching up slowly but fully once or twice so that he is lying on the back of the head and the buttocks.

REFERENCE

1 Gervis, W. H., *Orthopaedics in General Practice*, 1958. Heinemann Medical Books Ltd., London.