REFRESHER COURSE FOR GENERAL PRACTITIONERS

MEDICAL RELIEF OF PAIN

BY

E. J. WAYNE, M.D., F.R.C.P.

Professor of Pharmacology and Therapeutics, University of Sheffield; Physician, United Sheffield Hospitals

Pain is the commonest symptom for which a patient seeks advice, and a practitioner is often judged by the extent to which his treatment provides relief. It is, of course, only justifiable to treat pain symptomatically after every attempt has been made to discover its cause. The conditions which give rise to pain are many, but the mechanisms through which they act are comparatively few. Thus pain may arise in smooth muscle either from spasm or from overstretching. It may be caused by direct pressure on various parts of the nervous system. But perhaps the commonest cause is the direct irritation of nerve endings by chemical substances, such as hydrochloric acid in peptic ulcer or Lewis's P factor in muscle ischaemia. Clearly, different methods of treatment must be adopted in these different instances, and when the exciting cause is known it is often possible to use specific remedies. Thus spasmolytic drugs such as belladonna may bring relief to the sufferer from a spastic colon, and nitroglycerin remains the best remedy in the treatment and prophylaxis of attacks of angina of effort. Pain due to bacterial inflammation can usually be removed by the appropriate chemotherapeutic agent.

Unfortunately, however, in many cases the exciting cause cannot be discovered, and even when it can be found non-specific treatment may be the only practicable form of therapy, as, for example, in an attack of myocardial infarction or in inoperable carcinoma of the lung. It is then that the practitioner turns to drugs which depress the central mechanism for the appreciation of pain, and it is with these that I shall mainly deal.

Physical Methods for the Relief of Pain

Nevertheless, the more simple physical methods and the group of counter-irritant drugs should not be forgotten. It is quite easy to apply heat in the home by using hot-water bottles, electric blankets, or the ordinary bowl of electric fire; the greater relief afforded by the more elaborate methods used in departments devoted to physiotherapy is often in part due to psychological mechanisms. It should be remembered that the application of cold sometimes gives greater relief than that of heat, and an ice-cold compress or an evaporating lotion may be worth a trial in treating bruises or sprains.

Counter-irritant drugs are less used now than formerly, but they give undoubted relief in appropriate cases—for example, painful lesions in muscles, tendons, and joints. It will be appreciated that they all act through essentially the same mechanism—the release of histamine or some closely allied substance—and they differ chiefly in the intensity and duration of their action. It therefore seems reasonable to choose those substances which do not cause serious damage to the skin and which are relatively cheap. There is no evidence that liniments containing aconite, belladonna, or opium have any analgesic action on unbroken skin, and the simple liniments such as *linimentum saponis B.P.*, *linimentum album B.P.C.*, and *linimentum methylis salicylatis B.P.C.* are all satisfactory

preparations. The black ointment *unguentum iodi denigrescens cum methylis salicylatis* of the *National Formulary* has in addition to a counter-irritant action an impressive colour and smell.

The slightly soluble local analgesics such as benzocaine and orthocaine can be applied either as powders or ointments—for example, *unguentum benzocainae co. B.P.C.*—to superficial painful lesions such as ulcers, fissures, and mucous surfaces, but their action is short-lived and they may tend to retard healing. Sometimes they lead to a sensitization dermatitis.

An injection of procaine hydrochloride (as *injectio procainae et adrenalinae mitis B.P.*) into a localized area of tenderness in cases of non-articular “rheumatism” or tennis-elbow gives relief which may persist long after the action of the analgesic has worn off.

Use of Analgesic Drugs

In choosing from the large number of available preparations the practitioner must take into account the severity of the pain, as it is desirable wherever possible to use the less powerful drugs, for it is an unfortunate fact that the really potent analgesics all possess a tendency to habit formation.

Relative Efficiency of Analgesics.—Many methods have been used to test the relative efficiency of analgesic drugs, and it is perhaps not surprising that different results are obtained in the hands of different workers. Observations on animals in the laboratory are valuable as “sighting” tests, and information from human volunteers subjected to painful stimuli of varying intensity has added much to our knowledge of the mechanism of the relief of pain. Nevertheless, the clinician is bound to be more impressed by results obtained in human beings suffering from pain. The most striking finding which comes from observations in this field is that inert tablets and injections may be effective pain relievers. Indeed, in one trial inert tablets gave some degree of relief in 50% of patients suffering from pain of mild to moderate severity. Such results are not necessarily due to suggestion; they may be a measure of the tendency of pain to come and go, and the credit is thus given to whatever remedy is being taken at the time.

Choice of an Analgesic.—This usually lies between a member of the antipyretic group such as aspirin, a member of the narcotic group to which morphine belongs, and one of the newer analgesics—pethidine, amidone (“physeptone”), and phenadoxone (“heptalgin”). For severe pain such as that which arises from myocardial infarction or advanced malignant disease there is no fully satisfactory alternative to morphine. It is a remarkable fact that this drug, which was first isolated in 1816, is still the most widely used analgesic. It has a capacity to distract the attention and relieve anxiety possessed by no other substance. The effect resembles in some ways that of leucotomy; indeed, morphine has been said to produce a “reversible pharmacological leucotomy.” The newer analgesics relieve

pain effectively, but do not possess the sedative effect of morphine. It is clear that there are circumstances in which this is desirable, but most patients with severe pain prefer an opiate. The antipyretic analgesics are far less effective pain relievers, and presumably act at a different point in the central nervous system, for they produce neither euphoria nor addiction. Their safety is, in fact, their chief recommendation.

Antipyretic Group of Analgesics

A number of phenol derivatives have the property of reducing temperature and relieving pain, especially pain of so-called "rheumatic" type. They have no sedative effect and are not hypnotics, though they may induce sleep by suggestion. If, however, it is desired to produce sleep with certainty a hypnotic should be used in addition.

Aspirin.—In 1937 the annual consumption of this drug in the U.S.A. was 7,000,000,000 5-gr. (0.32-g.) tablets, and it is surprising that toxic effects are so seldom seen. In patients who have an idiosyncrasy to the drug, urticaria or asthma may be produced. Heavy dosage in anyone will give rise to tinnitus, deafness, nausea, or vomiting. On an empty stomach it may cause indigestion or even superficial erosion of the gastric mucosa. The tablets should therefore be taken crushed after food or in a soluble form. Prolonged use of aspirin and other salicylates may lead to hypoprothrombinaemia and the risk of haemorrhage.

Phenacetin is a useful alternative to aspirin because it does not irritate the gastric mucosa. Rarely it may cause methaemoglobinaemia and cyanosis.

Amidopyrine is the most powerful member of the group and is still widely used on the continent of Europe. It can, however, give rise to agranulocytosis, and though the risk is small it should not be undertaken. It is unfortunately still a constituent of some proprietary analgesic tablets.

Sodium salicylate is unpalatable and is a relatively ineffective analgesic except in acute rheumatism. In this condition it should be given in large doses—for example, 90 to 180 gr. (6 to 12 g.) a day.

Morphine Group of Alkaloids

Morphine has certain drawbacks, but in spite of these it is still the most widely used member of the group. At least 30% of individuals experience nausea after its use and more than 10% vomit. It may give rise to constipation, and full doses easily produce respiratory depression.

Diamorphine (heroin) should be used with great caution. The maximum pharmacological dose of $\frac{1}{8}$ gr. (8 mg.) is equivalent to more than $\frac{1}{2}$ gr. (32 mg.) of morphine. It gives rise to less vomiting or constipation than morphine but to much greater euphoria. Its liability to cause addiction has led to a complete prohibition of its importation and manufacture in the U.S.A., and its use in this country could be with advantage reduced and restricted to parenteral administration.

Dihydromorphinone ("dilaudid") has less sedative action than morphine, and its duration of action is shorter. It has the merit of causing less nausea than morphine, and is useful in conditions such as myocardial infarction and abdominal emergencies where the emetic action of morphine is especially undesirable. It is very apt to cause addiction. The usual dose in the adult is $\frac{1}{32}$ to $\frac{1}{16}$ gr. (2 to 4 mg.).

Codeine is a safe drug and is very unlikely to produce addiction. It rarely gives rise to vomiting, but may constipate. It is unfortunately a weak analgesic even when given in full doses of 1 gr. (65 mg.), and its main use is as a depressant to the cough centre.

Methyl dihydromorphinone ("metopon") has recently come into prominence in the U.S.A. and may become available in this country. Its great advantage is that it has less tendency than morphine to produce alimentary symptoms and mental dullness. Tolerance and dependence develop less rapidly, and it is effective when given orally. Its use should be restricted to cases with severe pain—for example, terminal cancer. It is apt to cause severe respiratory depression. The oral dose is $\frac{1}{10}$ to $\frac{1}{7}$ gr. (6 to 9 mg.).

Papaveretum and similar proprietary preparations—for example, "omnupon"—consist of mixtures of the purified alkaloids of crude opium. Controlled trials showed no difference between their effects and those of morphine.

The Newer Analgesics

Several new synthetic analgesics have been discovered in recent years. Only those which are available in this country are described.

Pethidine ("dolantin," "demerol," "meperidine" U.S.P.). This substance has a definite analgesic action, the intensity of its effect lying between that of the aromatic analgesics and of morphine. It has a slight local analgesic action, and drowsiness may occur after full doses. It has an antispasmodic effect on smooth muscle, and it is the combination of this action with its capacity to depress the perception of pain that makes it specially valuable in intestinal colic. It may, however, be used to relieve pain of any type, and has been widely employed in obstetric practice and pre- and post-operatively. It is less likely than morphine to produce unpleasant side-effects, but with doses of 100 mg. or more many patients complain of dizziness, nausea, or sweating. In prolonged overdosage or acute poisoning atropine-like effects predominate—for example, dilated pupils, dry mouth, tachycardia, and convulsions. There is, however, a wide margin of safety. Although a dose of 25 mg. ($\frac{1}{4}$ gr.) will often give an effect, the usual certainly effective dose is 100 mg. ($1\frac{1}{2}$ gr.). The duration of its action is less than that of morphine, but it is advisable that not more than 6 gr. (400 mg.) should be given in 24 hours. Tolerance does not easily develop, but an increasing number of cases of addiction have been reported, and it has been included with drugs scheduled under the Dangerous Drugs Act.

Amidone ("physeptone," "methadon," "miadone," "dolophine").—This is an effective analgesic with approximately the same pain-relieving effect as morphine, so that 10 mg. ($\frac{1}{6}$ gr.) is roughly equivalent to 10 mg. ($\frac{1}{6}$ gr.) of morphine. There is, however, considerable individual variation in response, and single doses as high as $\frac{1}{2}$ gr. (32 mg.) may be given. It differs from morphine chiefly in that it has a lesser tendency to produce nausea and vomiting and that it gives rise to less mental dullness. These may be great advantages, but the narcotic effect of morphine is sometimes desirable, and can be partly imitated by combining the drug with a short-acting barbiturate. Amidone is of value in most forms of pain, especially if the patient wishes to remain in full possession of his faculties. Its side-effects are, in order of frequency, dizziness, nausea, dryness of the mouth, sweating, and mental depression. They occur in about 10% of patients and are much commoner in individuals

who are not confined to bed. Amidone has a depressant action on the respiratory and cough centres, and often controls cough in doses as low as 2 mg. (1/30 gr.). It has a small margin of safety, and its use in children, especially as an elixir, is undesirable. For the relief of pain a dose of 5 mg. (1/12 gr.) should be tried initially, but the usual effective dose is 10 mg. (1/6 gr.). Addiction is less likely than with pethidine, but can occur. It has been shown that amidone will alleviate the symptoms of morphine withdrawal. It also has been included in the drugs scheduled under the Dangerous Drugs Act.

Phenadoxone (heptalgin).—This drug is chemically closely related to amidone, and tests based on its capacity to relieve the pain of muscle ischaemia indicate that it is at least as active an analgesic, weight for weight. Clinical experience, however, suggests that it is less effective. It has not been as fully investigated as amidone, but it seems probable that it has fewer side-effects, although in full doses it causes drowsiness. It is said to be less depressant to the respiratory centre. Phenadoxone is given orally in doses of 5 to 30 mg. (1/12 to 1/2 gr.) or by injection in doses of 10 mg. (1/6 gr.). It should be combined with a barbiturate if sedation is required, and it should not usually be given to patients who are out of bed. Phenadoxone gives rise to mild euphoria, but so far addiction has not been reported. It is scheduled under the Dangerous Drugs Act.

Combinations of Analgesic Drugs

There is probably no other field of therapy in which the phenomenon of alleged synergism has been so widely exploited by the manufacturers of proprietary remedies. Combinations of the antipyretic analgesics may sometimes be justified, since their toxic effects are different, and it is conceivable that the addition of caffeine or codeine may enhance the efficiency of the preparation. One such preparation—the compound tablet of codeine *B.P.C.*—is an imitation of a well-known proprietary remedy. It contains 4 gr. (0.26 g.) each of aspirin and phenacetin and 1/8 gr. (8 mg.) of codeine phosphate. It should be noted that the compound tablet of codeine contains in two tablets a greater total dose of analgesic than three tablets of aspirin or phenacetin; the alleged greater efficiency of this and other preparations over that of aspirin may be merely a question of dosage.

As pain is so often accompanied by insomnia, it is not surprising that many attempts have been made to imitate the action of morphine by combining the aromatic analgesics with barbiturates. These themselves have a very poor analgesic effect unless given in doses sufficient to cause unconsciousness, although there is some evidence that they may potentiate the pain-relieving actions of analgesics. The objections to such preparations are twofold: (1) some contain amidopyrine as the analgesic constituent; and (2) the barbiturate is often one of the longer-acting group, such as barbitone itself, and as the effect of the analgesic is as a rule short-lived, and the dose therefore often repeated, a cumulative effect may easily occur. It is always preferable to administer the analgesic and the hypnotic separately, so that the dose of the former can be repeated without necessarily at the same time giving a further dose of hypnotic.

Conclusion

The practitioner has thus a very wide choice of therapeutic methods when faced with the problem of pain. Those who wish to explore for themselves the newer

analgesics would be well advised to try amidone or phenadoxone by mouth as an alternative to morphine. The evening dose can be accompanied by a barbiturate. Such treatment may allow the patient to remain relatively aware of his surroundings during the daytime, and there is only a slight danger of producing addiction. Constipation is less likely to occur than with morphine. Pethidine is specially valuable in cases with smooth-muscle spasm and in obstetric practice. It now seems unlikely that a satisfactory alternative to morphine will be discovered which does not tend to give addiction. It is, however, probable that substances may yet be discovered which have fewer side-effects than the present analgesics and thus may approximate more closely to the "ideal analgesic" of the pharmacologist.

EUROPEAN COMMITTEE FOR MENTAL HYGIENE

The seventh conference of the European Committee for Mental Hygiene was held at Vevey, Switzerland, from August 30 to September 3. Dr. André Répond, the Director of the Mental Health Services for the Canton of Valais and past president of the World Federation for Mental Health, presided. This was the first conference to be held since the war, the last having taken place at Lugano in June, 1939. There were some 70 members and delegates from 13 countries, including Great Britain, Italy, Austria, and Western Germany. On the first day representatives from the 13 countries gave an account of the mental health services in their countries, and on the second day reports dealing with the special problems of mental hygiene occurring in various groups of countries were presented by Dr. Doris Odium for the English-speaking countries, Dr. Y. Porcher (Paris) for the Latin countries, Professor Dr. H. Schulte (Bremen) for Central Europe, and Professor P. Reiter (Copenhagen) for Scandinavia.

Dr. RONALD HARGREAVES, the chief of the Mental Health Section of the World Health Organization, gave a brief report on the concept of mental hygiene in that organization. In W.H.O. they held the view that mental hygiene could play the same role in the sphere of mental health and disease as physical hygiene played in the physical sphere. The doctor's role in mental as in physical hygiene was to treat the sick and to make researches into the nature and causes of mental illness and mental deficiency. The reduction of the incidence of mental disorders of all kinds and of mental deficiency could be achieved only through the activities of those who were dealing with the causative conditions in the general population—that is to say, public health authorities, teachers, ministers of religion, and, indeed, all those who dealt with the development and welfare of other human beings.

Geographical Variation in Incidence of Psychoses

As a result of special surveys it had been found that in Italy, although there was a high consumption of alcohol, there was a very low incidence of alcoholic psychosis, but this was not the case in certain other European countries. In Northern Sweden there was a high incidence of schizophrenia in relation to other psychoses, whereas in South Sweden manic-depressive psychoses predominated. In tribalized Africans, only the men have manic-depressive psychosis, and even this usually occurs only in those who are doing jobs of the kind that are usually carried out by and in association with white men. Even the limited amount of research which had already been undertaken showed how greatly the problems varied between country and country, and how essential it was to understand the fundamental causes and the contributory factors before either advocating or taking measures to deal with them. By means of child psychiatry and developmental psychology it might be possible to discover these basic factors. From the point of view of