REVIEW ARTICLE

ANALGESICS: SOME DEVELOPMENTS

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Introduction

At a time which Dale has called the golden age of therapeutics, when chemotherapy is making one spectacular advance after another, it is still important to remember how much of medicine is concerned with the treatment of symptoms. The relief of pain will of course follow the cure of the disease, but this may be slow while the pain is urgent and the ætiology still obscure. Analgesics may be defined as drugs which reduce or relieve the sensation of pain without producing loss of consciousness or parallel depression of other senses. Thus general anæsthetics, while used at times, as in labour, for escape from pain are not true analgesics nor are they desirable in the everyday treatment of pain.

Local anæsthetics are also now of established value in the treatment of such localised trouble as fibrositis, and skilled and experienced practitioners can often give remarkable and sustained relief by such injections. There has been some use of local anæsthetics intravenously in the relief of pain. This is difficult to justify pharmacologically, for these drugs, apart from cocaine, which is manifestly unsuitable for such application, are rapidly cleared from the blood-stream and fail to follow the Hughlings Jackson "law" in their action. Instead of the usual descending paralysis produced by narcotics—descending in the sense that the most recently developed and highly specialised functions of the central nervous system are the first to be depressed—intravenous local anæsthetics are quite liable to paralyse respiration in doses which scarcely affect spinal reflexes. It is true that analgesics similarly break the "law." Adrian[1], while doubting whether pain is as much appreciated at the level of the thalamus as Head maintained, agrees that since . . . "Pain needs no learning to increase its potency. This must be due to a direct effect on the basal ganglia." Analgesics should therefore act at this level as on the cerebral cortex, but while there is presumptive evidence of selective effects, there is need for something like tracer technique to establish real localisation of drug action. Probably by introducing a radioactive isotope into the analgesic molecule, the concentration of the drug could be estimated in the tissues even in great dilution, and its fate followed.

Methods of testing the potency of analgesic drugs are numerous. Where long series of related compounds have to be compared, some animal screening is first necessary. The promising drugs may then be assessed comparatively on human volunteers, as in a recent paper by Prescott *et al*[2]. Probably even such results in man require checking by

experience in the actual relief of human suffering before much weight can be attached to them.

Screening tests have been carried out on all sorts of laboratory animals, and a variety of painful stimuli have been tried of which heat in one form or another has been most popular because of the precision with which it can be repeated and measured. It is important that the intensity and duration of the stimuli should be such as to cause no tissue damage, since such would inevitably lead to changes in threshold. Fortunately there is no need for stimuli of such severity. In assessing possible analgesic value the toxicity of the proposed remedy and any side-actions which it may elicit must be taken into account, but it may not be possible to appreciate such considerations till clinical trials are instituted. In man, heat may be applied, till pain is felt, by the use of a resistance coil or by focusing the light of a powerful lamp on a fixed area of blackened skin. Other methods preferred by some workers for the study of analgesic action consist of assessments of the modification of the pain which the drug affords when pain is elicited by injections of hypertonic saline or by muscular contraction in an ischæmic limb. These and other methods are listed with numerous references in the recent chemical review of the synthetic analgesics by Bergel and Morrison[3]. There is abundant evidence that there is liable to be a large psychological element and a substantial individual variation in all such assessments, so that rigorous controls are necessary.

While analgesics have been shown to be very active when applied to the mid-brain directly, in quite small doses, the precise mechanism of their action is still unknown. Unlike most narcotics, analgesics have little effect on the oxygen consumption of the brain slice and little effect on choline-esterase systems, but they may block the availability of amino acids or other essential metabolites to certain nerve-cells.

Opiates

Opium has been used in the relief of suffering for at least three thousand years. It is nearly 150 years since morphine was isolated from opium. Yet as recently as 1938 Fourneau[4] claimed that morphine and a few of its derivatives could alone be considered true analgesics. The coal-tar antipyretics, widely used for certain nerve and muscle pains, seemed so far behind opium in the relief of pain associated with organic disease that Fourneau suggested they be called " antalgics," while he called cannabis and the related tetrahydro-cannabinols " euphorigenics," euphoria being the most striking part of the effects they normally produce. The hemp drugs have a definite analgesic action in animals but, rather curiously, increase in dosage does not enhance this analgesic effect. (Davies, Raventos and Walpole[5].) They have a long history in therapeutics, and the synthetic compounds may bring them again to the fore (Macdonald[6], Avison, Morrison and Parkes[7]). While cannabis is scheduled with the dangerous drugs and is known to be a frequent drug of addiction it is claimed to be free from any such risk in therapeutics, but its applications there have been so wide that one hesitates

to accept them. Its value in the amelioration of mood in mental disorders appears to be established.

The literature of the opiates is enormous, and no attempt to review it can be included here. The United States Public Health Services cover it in two large volumes (Kreuger, Eddy and Sumwalt[8]). In experimental animals, the action of opium and of total opium alkaloids is substantially the action of the morphine they contain. Potentiation by the other alkaloids is hard to demonstrate, and so is potentiation by neostigmine, though this has been claimed. Such use of a choline-esterase inactivator is the more revolutionary in that for many years it has been customary to give atropine or hyoscine with morphine to reduce its side-actions if not to enhance its analgesic effects. Many experienced physicians use morphine almost exclusively.

Many workers have published tables in which the analgesic activity of a series of drugs is assessed numerically in terms of morphine. Such tables may be misleading. Here let it be stated that the ideal analgesic is not established by a claim that it is, say, six times stronger than morphine. Morphine is usually strong enough. What is wanted is a drug which has morphine's anxiety- and pain-relieving qualities together with less or none of its undesirable side actions. Morphine lies open to criticism in that it is liable :—

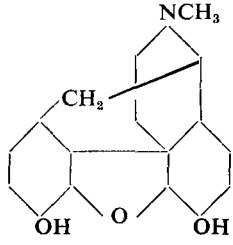
(1) to depress respiration.
(2) to produce nausea and vomiting.
(3) to be constipating.
(4) to produce tolerance and the chance of addiction.
(5) to increase itching and skin irritation.
(6) to be dangerous in susceptible subjects and young children.

A substance like codeine (methylmorphine) though it has only $\frac{1}{6}$ or less of the analgesic power of morphine, is often preferred because of its relative freedom from these side-actions. Diamorphine (diacetylmorphine) on the other hand, though a powerful and reliable analgesic, leads to habit formation so frequently and so quickly that its manufacture and importation are forbidden in the United States. There is a considerable movement to ban it similarly here, because of recent evidence of increased consumption and increasing addiction in various other countries. Mono-acetylmorphine is about four times as active as morphine when assessed by the methods of Hardy and Wolff (irradiation of blackened skin) or Smirk and Alam (pain produced by exercise of ischæmic limb), yet produces only "a moderate euphoria," much less nausea and vomiting, and allows of increased voluntary muscular effort in the presence of severe pain.

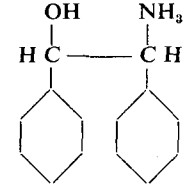
Dihydromorphinone (Dilaudid), and methyldihydromorphinone (Metopon), are in the diamorphine class or better as regards relieving pain. They are effective in the late stages of malignant disease, and good by mouth, but their actions are short and they may certainly provoke addiction.

The attempts to modify the structure of morphine in such a way as to relieve it of its side-actions but retain its analgesic value cannot be

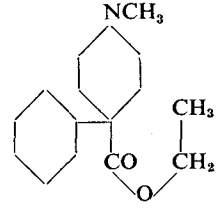
said to be strikingly successful though much research has been directed to this problem. Where the chemist has been successful in increasing the analgesic action by his manipulations, his product has usually shown increased toxicity, though not always a parallel increase in the two actions. As a rule the increase in potency is accompanied by a decrease in duration of action. Many regard the search for an analgesic which is not a potential drug of addiction as futile, but there is a sustained effort to find a morphine substitute which is less depressant to the respiratory centre. The failure so far to synthesise morphine in spite of attempts by many distinguished chemists has probably been a major difficulty but Gulland and Robinson[9] here and Grewe[10] in Germany have made marked progress. There is an alternative method of investigation—to try and identify the basic part of the morphine molecule with which analgesia is associated and then test various chemical modifications of this for potency.



Morphine.



β-Hydroxy-α;β-diphenylethylamine.



Pethidine.

This is the technique so successfully followed by Dodds[11] in the development of the synthetic œstrogens. In the case of morphine he believed that diphenylethylamine was the core of its efficiency, and tested 18 compounds by the Hardy-Wolff and other techniques. Peak activity was found in hydroxydiphenylethylamine, which gave " complete relief in doses of 200 to 400 mg. four hourly." At first this looked promising but later it appeared that many forms of pain were uninfluenced by these drugs though in malignant disease they were claimed to be of special value. In comparative tests in animals they show no significant activity.

PETHIDINE

Pethidine was introduced (Eisleb and Schaumann[12]), not as an analgesic but as a spasmolytic. Its original name was Dolantin, and it was introduced here as Dolantal, in America as Demerol. Its ability to

relieve pain was discovered later, and its rather remote chemical relationship to morphine suggested. Though as an analgesic it seemed to be in the codeine rather than in the morphine class, (Woolfe and Macdonald[14]), the facts that it had any real pain-depressing activity and that it provided a convenient molecule for modification by the synthetic chemist gave a fresh impetus to research in analgesia. Pethidine was the best of Eisleb's compounds as assessed by Schaumann[13]. A long series of related compounds synthesised by Bergel and his team were assessed pharmacologically by Macdonald and Woolfe[15]. Some had a longer action on mice than pethidine and some had a slightly stronger action—notably 2'-methylpethidine—but although certain of these derivatives received some clinical encouragement (Glazebrook and Brantwood[16]) the differences were not sufficiently great to be very important. Since then an ethyl ketone, Hoechst No. 10720 (ketobemidone) has been claimed to be ten times as active as pethidine, and has had a promising clinical trial (Kirchhof[17]).

Pethidine is of established value in relieving the pain of labour, and this may be related to its additional action as a spasmolytic. When combined with gas and air in doses of 100 mg, to 200 mg., however, it is reported to double the incidence of asphyxia neonatorum and the same risk is recorded on a much larger series when used with trichlorethylene[18].

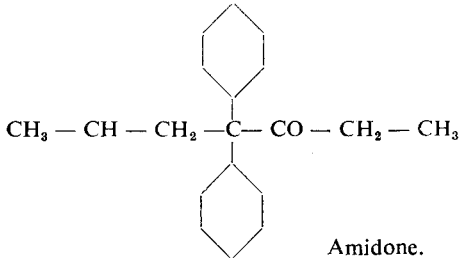
Is it therefore concluded that the routine use of pethidine by midwives cannot be approved. Whether the disadvantages of pethidine can be avoided in the new compound ketobemidone (Hoechst 10720) or in some of the heptanones or hexanones is still uncertain. The demand for a safe and reliable analgesic for use in the conduct of labour is insistent, and the use of inhalers for nitrous oxide or trilene without premedication seems to be reasonably satisfactory in some eighty per cent. of cases. This problem is now receiving widespread attention.

Amidone and Related Compounds

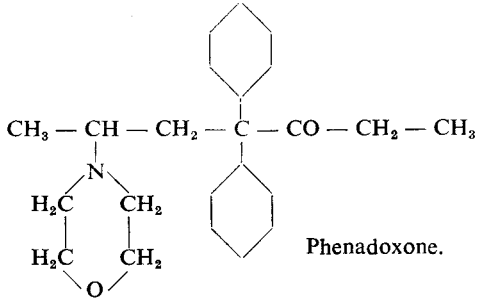
Amidone (Hoechst 10820) also known here as miadone and physeptone, and in America as methadon, adanon and dolophine, was revealed during the investigation of I. G. Farbenindustrie[19] at the end of the war. This compound again stimulated a fresh outburst of research. It was found to be at least as powerful an analgesic as morphine, yet less hypnotic. Its use however is often complicated by prolonged nausea and vomiting, and today it may be more important as a source of new compounds which may retain analgesic efficacy yet be free from these unpleasant side actions. Of such *iso*amidone, which was discarded by the original Hoechst workers has had favourable reports both here and in America[2,20] and 2-dimethylamino-5-acetoxy-4 : 4-diphenylheptane and the 2-morpholinopropyl compound (C.B. 11) are relatively free from unpleasant toxic effects.

It is a pity to find the latter (Phenadoxone, Heptalgin,) advertised as " activity six times that of morphine " even if certain animal tests confer such a ratio. It is much more important to be assured that the acute

toxicity is relatively much lower and that side effects apart from mild drowsiness with full dosage are negligible. Relative freedom from serious respiratory depression and constipating action is freedom indeed.



Amidone.



Phenadoxone.

Wilson and Hunter[21] comparing amidone, phenadoxone, and pethidine found that 5 mg. of amidone only relieved ischæmic pain in six of ten subjects, whereas 5 mg. of phenadoxone relieved nine of the ten. Both were better than 50 mg. of pethidine, but this was strikingly more euphorigenic than the newer drugs.

The optical isomers of amidone have been prepared (Thorp *et al.*[22]) and compared with the racemic forms (Thorp[23]). The lævo-isomer is responsible for the effects of amidone on the central nervous system, while the dextro compound shares equally in the spasmolytic, local anæsthetic and toxic actions on the circulation (but not on the respiration) in experimental animals.

No important recent developments have taken place in Fourneau's " antalgics." Amidopyrine is probably still the most potent but has lost favour because of its occasional effects on the bone-marrow. Aspirin is still the most widely used, yet phenacetin is regarded by critical observers as a more effective drug, though little used by itself. These two, in combination with a little codeine, at present enjoy an enormous vogue but there is some doubt whether the claimed " potentiation " in such mixtures will bear pharmacological scrutiny.

The barbiturates which were at one time claimed to be analgesic as well as hypnotic have failed to live up to any such claim except in anæsthetic doses—the use of the shorter-acting compounds as intravenous anæsthetics is undoubtedly a major advance. The barbiturate-antalgic combination, so bitterly opposed in the past by Willcox, has been

restricted by the inclusion of barbiturates in Schedule IV of the Poisons Act and by the wide publicity given to the toxic risks of amidopyrine which is similarly scheduled. Wayne[24] has recently emphasised the risks involved in the abuse of such drugs.

Most new analgesics, whether related to morphine or not, have been introduced as "free from morphine's tendencies to produce tolerance and addiction." None has seriously stood up to critical tests of such claims—perhaps it is too much to expect of an analgesic. But the advances in this field in the past ten years are full of hope and promise, and whether an approximately ideal drug will be provided by the acetylated alcohols corresponding to the ketones of the amidone group, by some other derivative or in some quite different way, it will surely be found in due course.

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