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SOME NEW ASPECTS OF THE ACTION OF MORPHINE-LIKE ANALGESICS*

BY

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In 1941 Krueger, Eddy, and Sumwalt published a review on the pharmacology of morphine and summarized the world literature on this subject. It was an admirable achievement. They collected the evidence from more than 9,000 publications and condensed it into a volume of 800 pages. Considering that the analgesic action of morphine is by far the most important of its effects, it is surprising that only 9 of these 800 pages were concerned with analgesia and that only 30 of the 9,000 references dealt with its experimental investigation. More than 99% of the work was devoted to the so-called side-effects.

There is a simple explanation for this strange disproportion. Until 1939 morphine and some of its derivatives, such as heroin, "dilaudid" (dihydromorphinone hydrochloride), and "eukodal," were our only powerful weapons in the struggle against pain. The clinical experience with these drugs was sufficient to evaluate their analgesic potencies. The mechanism of analgesia was explained by the rather vague assumption of an action on the central nervous system. In their review Krueger *et al.* wrote: "Analgesic action is predominantly central, though recent work advocates a peripheral component. Its site and mechanism have not been determined. Nor has the mechanism of narcotic action been ascertained." This statement was made in 1941.

Measuring Analgesic Potency

After the discovery of synthetic substitutes for morphine much more work was devoted to the study of analgesia. Between 1939 and 1942, after the discovery of pethidine (Eisleb and Schaumann, 1939), innumerable substances have been synthesized in the laboratories of the Höchster Farbwerke by varying the chemical structure of active drugs (Kleiderer, Rice, and Conquest,

1945). The pharmacologist was thus faced with the task of looking for analgesic activity in hundreds of compounds and of comparing the potencies of the active derivatives.

This requirement was met by about 50 different methods for measuring analgesia which have been elaborated within the last 10 to 15 years. The purpose of these methods was to provide exact figures for the analgesia produced and to allow a statistical evaluation of the results the accuracy of which could be relied upon.

Nowadays this kind of work is a little overdone, particularly when analgesic potencies are determined up to the second decimal place with well-defined fiducial limits. Often the possibility is overlooked that the values obtained are not the result of analgesia but are due to other factors—for instance, to changes in blood flow. Many workers are not disturbed by the fact that their results are inconsistent with those of other authors, so long as the validity of these results is proved by statistics. In Table I the analgesic potency of pethidine

TABLE I.—Relative Analgesic Potency (Morphine = 1)

	Experimental	Clinical
Pethidine		
Author 1	0.135	} 0.15
" 2	0.45	
" 3	0.94	
Methadone		
Author 4	1.2	} 1.5
" 5	6.5	

Clinical doses: morphine, 15 mg.; pethidine, 100 mg.; methadone, 10 mg.
 Relative potency: morphine, 1; pethidine, 0.15; methadone, 1.5.

and of methadone, as tested by different workers, is compared with that of morphine. There is a wide variation in the ratios, and some of the figures are not in agreement with clinical experience. There is no reason to doubt the experimental results or the statistical evaluation of these different results. However, quantitative comparisons in animal experiments are obviously useful only if the results correspond to the experience obtained in man. Therefore, in many cases inadequate methods must have been used, a possibility not always realized.

Nevertheless, we have a number of reliable methods for measuring analgesia. The most subtle methods, however, are not necessarily always the best. As a historical demonstration I would like to tell you which instrument and which method I used in my discovery of the analgesic property of pethidine and in the determination of the analgesic potencies of methadone and of hundreds of other compounds. It was nothing but a forceps with which I pinched the tails of mice. Nevertheless, with this simple method I determined (Schaumann, 1940) the relative potencies of pethidine, methadone, phenadoxone, and ketobemidone, and the results have been confirmed by the majority of later investigators and by clinical experience. The method was actually described as early as 1929 by Haffner.

Criteria of Specificity

With the synthetic analgesics it became possible to separate the specific from the non-specific effects. An effect is specific if it is common to all analgesics whatever their chemical structure, and if the potency in producing the effect runs parallel to their analgesic potency.

Another criterion for the specificity of an action is its great sensitivity against small changes in the chemical constitution. If we exchange the N-methyl group in morphine or in levorphanol against an allyl group, we obtain two

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antagonists of morphine. The analgesic effect is also abolished by an exchange of the methyl group in the side-chain of methadone for an ethyl group. From pethidine, an active compound can be derived by substituting a hydroxy-group in meta-position, but inactive products result from substitution in ortho- or para-position.

A particularly striking example of the sensitivity of the analgesic effect to small changes in the chemical structure is the difference between the optical isomers of the same compound. This became clear when the synthetic products became available. The dextro-isomer of levorphanol, for instance, has no analgesic potency, and in methadone the dextro-isomer is 30 times less potent than the laevo-isomer.

This difference between optical isomers allows a clear-cut distinction between the specific analgesic effect of the morphine-like analgesics and general anaesthesia. The potency of general anaesthetics is determined chiefly by their solubility in lipids. Therefore there is no difference between the optical isomers. This has been shown for the optical isomers of the secondary butyl alcohol (Viditz, 1933; Butler and Dickson, 1940) and for some barbiturates (Kleiderer and Shonle, 1943). In local anaesthesia too, there seems to be no significant difference between optical isomers (Gottlieb, 1923; King, 1924).

A further criterion for the specificity of an effect of analgesic is the fact that it is abolished by nalorphine.

Thus there are four criteria which allow us to test whether an effect observed with one of the analgesics is specific or not: (1) the sensitivity to small changes in chemical constitution; (2) the difference in potency between its optical isomers; (3) the antagonistic effect of nalorphine; and (4) the parallelism between the potency in producing the effect and the analgesic potency.

Based on these criteria, there are the following specific effects of morphine-like analgesics: (1) analgesia; (2) the depression of respiration; (3) the effect on intestinal motility; (4) central excitation in cats and mice; (5) the hyperglycaemic effect; (6) the effect on body temperature; and (7) the liability to produce addiction.

It is therefore not correct to say that the depression of respiration and the constipating effect of the analgesics are side-effects. They are inseparable from their analgesic action. This is unfortunately also true for the liability to cause addiction. It will therefore not be possible to find morphine-like analgesics without this undesirable addition, and in fact all efforts in this direction have been unsuccessful.

Analgesics and Constipation

A great deal of work has been wasted on the constipation produced by analgesics. In their review of 1941 Krueger *et al.* devoted 136 pages to this action of morphine and quoted more than 200 references. Nevertheless, in summarizing the results they arrived at the following conclusion: "In spite of the many and extensive studies . . . it is clear that there are many gaps yet to be filled before a clear and complete account can be given of the effect of morphine on the gastro-intestinal tract." The reason for this unsatisfactory result is that the overwhelming majority of authors stuck to the same method (the Thiry-Vella fistula), to the same experimental animal (the dog), and to the same intestinal segment (the small intestine), and were apparently very pleased when they always obtained the same results.

It is not easy to oppose such a bulk of experimental work. I think that the many published tracings which show a rise in tone and an increase in motility of the intestine, however constructive and impressive they may be, only prove that the method is unsuitable to explain the constipating effect in man. The method is open to the following criticisms: first, morphine causes diarrhoea in the dog, therefore the dog is not a suitable animal; second, the Thiry-Vella fistula is not a normal intestine; and third, the small intestine is the least important part of the intestine for the constipating effect.

In my opinion, three factors are predominant in causing constipation after morphine (1) Suppression of the call for defaecation. It is an old observation that a patient under morphine with severe diarrhoea often notices the call for defaecation for the first time only when the fluid has reached the skin. (2) Inhibition of the defaecation reflex. In rabbits (Eddy, 1932; Emerson and Moodey, 1935; Karr, 1947; Scott *et al.*, 1947) and rats (Schaumann, Giovannini, and Jochum, 1952) the number of faecal balls which appear per unit time diminishes, and this diminution runs parallel to the intensity and duration of analgesia (Table II). (3) Inhibition of propulsive motility as by the peristaltic reflex, especially in the large intestine.

TABLE II.—Rat, Number of Scybala

	Dosage (mg./kg.)	No. of Scybala During		
		1-3 hours	4-6 hours	7-9 hours
Control ..	0	4.4	3.2	2.3
L-Methadone ..	0.1	2.9	3.2	3.3
	0.5	1.4	3.0	5.2
	1.0	0	4.0	5.0
D-Methadone ..	1.0	3.5	4.1	3.4
	5.0	1.4	4.0	4.6
	10.0	0.8	3.0	4.3
Morphine ..	0.2	2.5	1.0	2.5
	0.5	1.7	4.2	5.1

Nearly all authors accept the theory of a spastic constipation with increased intestinal motility. In my opinion it is unlikely that this occurs. According to Vaughan Williams and Streeten (1951), morphine spasms in the small intestine of the dog can be overcome by 19 cm. water pressure; the force of the peristaltic wave, however, is at least 15 to 20 times stronger. As everybody knows from his own sad experience, even the anal sphincter is no safe barrier against an oncoming peristaltic wave.

So far I have dealt with the specific effects. The unspecific actions are: their toxicity to animals, spasmolytic effects on smooth muscle, local anaesthesia, and inhibition of certain enzymes. These effects are unspecific because they do not run parallel with the analgesic power of the analgesics, because there is no difference between the optical isomers, because they are not antagonized by nalorphine, and because they occur also with compounds of entirely different chemical structure.

Toxicity

A few more words about toxicity. It can be seen from Table III that there is no constant relation between analgesia and toxicity. Pethidine is about seven times weaker than morphine in producing analgesia, but is twice as toxic for mice. D-methadone is just as toxic as its L-isomer, although its analgesic potency is 30 times weaker. In man the situation is different, because in man toxicity is determined by the depressant effect on respiration. It is therefore not possible to calculate a therapeutic index for use in man from animal experiments. Otherwise the clinical use of pethidine would be criminal, since it has a 15 times lower index than morphine in animal experiments. However, clinical experience has shown that the contrary is true, or pethidine would not have displaced the use of morphine in general anaesthesia to the extent it has.

Paradoxically we might even say: the greater the toxicity of a morphine-like analgesic in mice in comparison to its

TABLE III

	Toxicity (Mice subc. inj.)		Analgesia (Morph=1)	Analgesia/ Toxicity Therapeutic Index (Morph=1)
	(mg./kg.)	(Morph=1)		
Morphine ..	400	1	1	1
Pethidine ..	200	2	1/7	1/14
D,L-Methadone ..	42	10	2	1/5
Phenadoxone ..	200	2	3	1.5
L-Methadone ..	35	11	3	1/3
D-Methadone ..	50	8	1/10	—

analgesic potency, the smaller is the danger of respiratory failure in man. The depression of respiration is antagonized by the central excitatory effect which in mice causes lethal convulsions. Therefore a low therapeutic index in animals means less danger in man. It is also a strange and paradoxical fact that in man the smallest overdoses are the most dangerous in morphine poisoning and that the mortality decreases with increasing doses. Krueger *et al.* have compiled some 200 cases of morphine poisoning from the literature with the following result: with doses from 60 to 600 mg. there was a mortality of 25%; with doses from 700 to 1,200 mg. the death rate went down to 6%; and with enormous doses from 1,500 to 7,200 mg. it reached only 15%. The highest known doses administered—that is, 4.5 g., 4.8 g., and 7.2 g.—were not fatal. Tatum, SeEVERS, and COLLINS (1929) found the same paradox in monkeys: with 20 to 150 mg./kg. the mortality was 27%, and the fatal effect was due to depression; with doses from 200 to 300 mg./kg. there were no alarming symptoms, and doses of over 500 mg./kg. caused convulsions and death.

The parallelism between the specific actions suggests that a close relation exists also so far as their site and mechanism of action are concerned. This in turn makes it likely that a close relation exists also between the apparently different physiological functions which are affected by the analgesics. In my opinion, this is really the case. All these functions have the common task of warning and protecting the organism against imminent damage; they exert a protective function.

The "Protective System"

There can be no doubt that pain in all its variations—from the subconscious (subcortical) pain reflex to the conscious experience of pain—has such a protective function. The reflex protects against damage of the tissue—just think of the decapitated frog pulling its leg out of an acid solution—and the experience of pain warns against imminent dangers. The morphine-like analgesics inhibit this protective function of pain by suppressing first the conscious experience of pain and in higher doses also the reflex response to painful stimuli.

In analogy, we must recognize a protective function in the regulation of respiration. It protects the body against acidosis. Apart from the subconscious autonomic regulation we have the warning sensation of dyspnoea which corresponds to the experience of pain and which can reach the terrible feeling of suffocation. Here, too, the analgesics block first the conscious sensation of dyspnoea, and finally, in higher doses, the subconscious, automatic regulation of respiration as well.

There is a similar safeguard concerning circulation. We have the regulation of blood pressure and the Bezold reflex. The disagreeable throbbing of the heart and the feeling of anxiety associated with stenocardia warn against imminent collapse by overstrain of the heart and may be compared to the sensations of dyspnoea and of pain. Again the morphine-like analgesics in therapeutic doses abolish the feeling of oppression, and in high doses the blood pressure regulation as well.

The effects on the gastro-intestinal tract and on the temperature regulation can be regarded in the same light. The analgesics first suppress the call to defaecate, then the defaecation reflex, and finally the entire propulsive motility. They first abolish the feeling of cold, then the shivering fit, and finally the whole system of temperature regulation.

These physiological functions can be separated from the rest of the autonomic regulations and from the epicritical system of sensual perception because of their special task and because of their specific sensitivity to the morphine-like analgesics. They can be considered together as forming what I have termed the "protective system" (Schaumann, 1954a, 1954b) (Table IV).

It is characteristic of this protective system that its different functions are brought into action by noxious stimuli and that in man they enter the psychic sphere. All these

TABLE IV.—Some Parts of the Protective System

Individual Function	Noxious Stimulus	Subconscious Regulations	Psychical Equivalent
Protection of tissue	Damage to tissue	Defence-reflex	Sensation of pain
Respiration	CO ₂	Hyperpnoea	Dyspnoea
Circulation	Over-strain	Bezold-Jarisch effect	Palpitations.
Digestive tract	Distension.	Peristalsis. Defaecation reflex	Oppression
Constancy of body temp.	T _{ox} stimulus Body temp.	Temp. reg.	Call to defaecation Feeling of cold. Shivering fit

separate functions are inhibited by the morphine-like analgesics in proportion to their analgesic potencies. Analgesia is therefore only one part of a general anti-protective action of the analgesics.

Doses of analgesics which suppress the dysphoric sensations connected with the functions of the protective system do not influence sensory perceptions like touch, taste, vision, and hearing and their mental assimilation. In this respect, analgesics contrast with general anaesthetics. The invaluable relief given by the analgesics rests on their ability to suppress the protective system with its dysphoric sensations and anxiety. When using analgesics we have to keep in mind that they inactivate this protective system, which serves the useful purpose of warning against injury. Therefore the use of analgesics should be permitted, or indeed ordered, only when the warning has been heeded or the functions of the system have lost their meaning.

We have also to remember that liability to produce addiction has its cause in the suppression of these tormenting sensations. The danger of becoming an addict will be particularly great in people who have an abnormally oversensitive protective system and who are troubled with dysphoric sensations by stimuli which are quite normal. These people must be regarded as being ill. Suppression of their over-active protective system at first results in the feeling of relief from their troubles; there is therefore the temptation to continue using analgesics, which in the end results in physical dependence. This is the reaction of the protective system against the depressing effect of the analgesics and becomes apparent in the form of the symptoms of withdrawal. The longer and the more intensive the use of analgesics has been, the stronger will be these symptoms.

Conclusion

When we gained our intellectual powers we lost paradise. We were enabled to enjoy all that is good, beautiful, and true, but we were also condemned to suffer pain, worries, and fear to an extent unknown to animals. But in addition we have been endowed with the mental powers and the free will to obey the warning voice of our protective system, or to stifle it when it becomes a senseless tormentor. If we are forced to stifle these promptings, the morphine-like analgesics are our most efficient weapons for the purpose.

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