EFFECT OF SOME NEW SYNTHETIC ANALGESICS ON GASTRO-INTESTINAL MOTILITY IN THE RAT AND RABBIT

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INTRODUCTION

The research studies described in this thesis are concerned with the comparative effects of a number of new narcotic analgesics on the gastrointestinal tract of the intact animal. To serve as a basis for comparison, morphine has been used as the standard drug. The purpose of this work has been to compare the constipative effects of these newer analgesics with morphine in an effort to find less constipating but still potent pain relieving agents. While such a study may seem, at first sight, to represent only a specialized phase in the over-all evaluation of new analgesics resembling morphine, further consideration will reveal that no single effect of morphine or other narcotics can be properly and intelligently appraised without taking into account their many diversified actions on the animal body. Moreover, while the constipative action of morphine is considered here as an undesirable "side-effect", it is realised that frequently morphine is employed in medicine for this single effect. Also, it is appreciated that other effects produced by morphine such as respiratory depression, sweating, itching, nausea and vomiting, dimness of vision, dizziness and other symptoms may occasionally prove more objectionable than constipation. Nevertheless, running through the history of man's attempt to find effective analgesic preparations free of objectionable untoward actions we find the problem of modifying the constipative effects of opium, morphine and, more recently, the synthetic analgesics being given foremost consideration. Only in the past few years has

this problem been superceded by that of finding ways and means to overcome the addictive properties of morphine.

In order to appreciate the efforts made in the past to provide medicine with potent pain relieving drugs lacking undesirable properties, and to understand the difficulties and barriers encountered in trying to achieve this goal, the following review of the historical development of opium and its narcotic alkaloids is offered. In this presentation major emphasis has been placed on the attempts to modify the constipative effects of opium and morphine, keeping in mind that these efforts often led to accentuation or lessening of the other effects, good or bad, of these drugs.

HISTORICAL REVIEW

I. A Review of Attempts To Provide Preparations Equal To Opium or Morphine in Analgesic Effect and Free of Objectionable Side-Effects.

Since antiquity medicinal preparations of opium from the oriental poppy have been used to compel sleep and relieve pain. Tainter (1948) (1) points out that the story of man's efforts to combat pain achieved early attention, beginning as thin threads of legend, fact, and fancy all winding their way through the mythology, culture and religious rituals of man's early civilizations. Even ancient Babylonian clay tablets, presumably dating from 2250 B.C., mention an analgesic remedy for painful dental caries.

As man's experience with preparations of the poppy progressed, it was realized that this substance produced a wide diversity of effects

on the human body and that these effects could be employed to treat a number of afflictions. The Ebers' papyrus (2) of about 1550 B.C. records many prescriptions containing the berry of the poppy (opium) recommended for coughs, for driving out pains or to stop a child's crying. However, none of the various remedies suggested for diarrhea in the Ebers' papyrus contained poppy berry. Biblical medicine closely parallels that of the Egyptians (2). Macht (1915) (3) cites the probable biblical references to opium, but states that the first authentic report of the use of opium is that by Theophrastus about 300 B.C. This statement is quoted extensively by present-day writers..

The de Medecina of Celsus (4) written early in the first century A.D. lists poppy-berry preparations and pills containing poppy-tears for such various purposes as to relieve pain, to promote sleep, to suppress coughing and to quiet restless children. A warning against untoward effects is implied in this formulary since it is recommended that some of the more potent opium pills be used only in overwhelming necessity. Spencer (4) expresses the observation that Celsus knew only the wild poppy (Papaver rhoeas) and the prickly poppy (Papaver argemone), but not Papaver somniferum, because he failed to include poppy preparations in his poison list. Later writers during this first century A.D. such as Scribonius Larges and Diascorides provided more definite instructions on the production, preparation and use of these opium drugs pointing out the adulterants used by unscrupulous merchants and warning of the dire results or even death resulting from overdosage. These latter writers reflect the greater understanding of the source of the

drug with consequent more efficient production, the selection of a high-yield species, the great commercial extent of its use and that considerable knowledge of the therapeutic and toxic properties of opium had been acquired during this century.

It is difficult to determine, however, whether or not these early medical records suggest that the constipative effects of opium were known or that constipation invariably resulted when the drug was used so that laxative substances should be employed to offset this effect. Nevertheless, sometime during the third or fourth centuries A.D. the constipative effects of opium were apparently appreciated as suggested in the writings of Arabian physicians. Indeed, during the Dark Ages it would seem that the main use to which opium was put by the Arabs was for the relief of dysentery and diarrhea, probably one of the most common disorders found among the peoples of Asia Minor in those times. Avicenna the Arabian physician, 980-1037 A.D. especially recommended opium for diarrhea (cited by Macht (3)). But, while the use of opium preparations progressed to the far east over the Arab trade routes where its chief use was to control dysentery, the other valuable medicinal uses of opium were either overlooked or considered of less importance.

With the advent of Paracelsus who heralded the medical Renaissance at the beginning of the sixteenth century, a revival occurred in the medicinal use of opium. Paracelsus introduced Laudanum (still retained as Tincture of Opium in the current U.S.P. XIV) which he prescribed freely and liberally for many conditions. Except for recommending some restriction in dosage in some afflictions, Paracelsus made no attempt

to alter the actions of his beloved Laudanum by the addition of adjuvants or correctives. Laudanum, in itself, seemed such a superior panacea to other preparations of opium that Paracelsus saw no reason to try to improve upon it. But, with widespread usage and the gradual influx of polypharmacy into apothecary medicine, it was soon discovered that the use of other substances along with opium would either enhance or diminish certain effects attributed to opium. Paregoric, named after Paracelsus, was introduced as a very palatable, sweetened and "de-bitterized" liquid preparation to supplant Laudanum for the treatment of a variety of conditions without causing as much constipation as Laudanum. Doctor Dover of England, around 1730 A.D., introduced his mixture of powdered ipecac and opium as a palliative remedy for upper respiratory conditions and the grippe. Through causing powerful diaphoresis and lessening bronchial irritation and cough, Dover's Powders proved an useful addition to the drug armamentarium of those days; in fact, it remained in the U.S. Pharmacopoeia up to 1945. Also introduced about this time was the mixture of opium and licorice known as Mistura Opii et Glycyrrhizae Compositae intended for the relief of cough; even today one finds this improved mixture of opium relied upon in large institutions as a cheap and effective cough remedy. Thus, by the use of adjuvants or correctives, it was found that it was possible to some degree to bring out certain desirable actions inherent in opium or to suppress those actions not desired in the particular condition being treated.

One hundred and fifty years ago, in 1805, Friedrich Wilhelm Adam Sertuerner (cited by Tainter (1)) first isolated the pure alkaloid,

morphine, from opium. It was hoped that this pure, white crystalline powder which Sertuerner named morphia after the goddess of sleep and solace from pain would be free from the other undesirable properties found in the parent substance opium. Yet, the intestinal side-effects of morphine prevented Sertuerner from using this potent analgesic later on in life when he was sorely afflicted with gout. Experience soon showed that while more powerful than opium in relieving pain or compelling sleep, it was also more likely to cause constipation and other undesirable side-actions. In fact, not until the introduction of the hypodermic syringe in the latter part of the nineteenth century did the use of morphine become popular in medicine. And then came the realization that this pure substance was much more likely to cause drug addiction, a condition which the physician had known was possible with the continued use of opium, but considered of little serious consequence in the medicinal use of this older drug. As the physician began to place more and more dependence on the use of injectable morphine for the relief of acute and chronic pain and other disorders, the realization grew that all too frequently the benefits to be derived from the use of morphine were more than negated by its addictive qualities. The search for substitute analgesics to replace morphine continued.

Towards the turn of the present century the other important alkaloidal fraction found in opium, codeine, was introduced in medicine. It was found suitable as an effective cough suppressant and while possessing some of the pain-relieving qualities of morphine, it also

produced the same untoward side-effects and, on continued usage was habit-forming. Heroin, a synthetically altered morphine, was introduced in 1911 as a non-addictive substitute to replace morphine but experience soon proved the fallacy of this optimistic claim with its banishment from medical use in this country. Nor have such refined injectable preparations of opium such as Pantopon(R) been found to be less addictive or freer of such untoward effects as constipation, respiratory depression, etc. than morphine. Dihydromorphinone hydrochloride (Dilaudid(R)) introduced from Germany in this country in 1934 while possessing the good features of morphine similarly retained many of the undesired and was found to offer little, if any, improvement over morphine. But a ray of hope was held out by the introduction of these synthetic derivatives of morphine in that, through slight alteration in the structure of the morphine molecule some of the dominant actions of morphine could be accentuated and others muzzled or held in abeyance, if not entirely eliminated.

Thus the goals of this search were more clearly defined: to develop, through synthetic chemistry, compounds retaining the desirable feature of morphine such as analgesia, cough suppression, or sedative action without at the same time manifesting the undesired properties of addiction and tolerance, respiratory depression, miosis and dimness of vision, sweating, constipation, etc. The object was to find a compound retaining the potent analgesic properties of morphine without the many side-effects being exhibited either at all, or, at least not to the same degree.

This challenge was met, in part, by the researches undertaken by a number of investigators in this country working under the auspices of the National Research Council (5). Over a period of ten years this group studied many newly synthesized compounds and our knowledge of the pharmacology and biochemorphology of morphine was enhanced by a wealth of significant observations and explanations. But, unless one excludes the new synthetic analgesic Metopon(R), this group was unable to provide a substitute for morphine.

It remained for the German workers, Eisleb and Schaumann (cited by Tainter (1)) in 1940 to show that compounds of a somewhat different chemical structure than morphine such as the phenylpiperidine esters could provide nearly as effective analgesia without many of the accompanying untoward effects. The drug they introduced under the name of Dolantin (Demerol(R), Meperidine, U.S.P., Isonipicaine) is a potent analgesic and less constipative or addictive than morphine. In 1945, at the end of World War II, it was found that the Germans had continued their investigations along this line and had discovered that another somewhat different compound than Demerol(R), which they called Amidone (Methadone, N.N.R., Dolophine(R)) also was an excellent analgesic and, while more constipating than Demerol(R), resembled morphine somewhat more closely in its other actions such as cough suppression and respiratory depression. Thus, through synthetic chemistry and the biochemorphologic study of the relation of chemical structure to pharmacologic activity, the pathway has been opened to man's long sought endeavor to find a way to retain the pain-relieving qualities of morphine

without its undesired features. We are now in the era of synthesising new compounds which retain these characteristics or chemical combinations and groupings in the molecule known to be responsible for effecting analgesia and of altering, by addition or subtraction, other parts of the molecule thought to contribute to certain undesirable actions of the compound. Then, through screening experiments designed to test these various actions on laboratory animals, data may be gathered to reveal the pharmacologic nature of these new compounds before selection of the most promising compounds for human trial. It is this part of the effort to develop effective substitutes for morphine which may lack, or be present to less degree, the undesirable property of causing constipation with which we are concerned here.

II. A Review of Methods Used to Study the Constipative Effects of Opiates and Related Analgesics in Man and Animals.

The problem of constipation from prolonged use of analgesics has been a bothersome one to practitioners of medicine for many years and has resulted in a great amount of study concerning the effect of analgesics on the intestine.

A. Physiological Aspects.

The magnitude of the problem may be appreciated by considering the evidence (6,7,8) that the intestinal tract has a basic or intrinsic muscular rhythm of inherent contractility and possesses many plexuses which have their own ability to modify the activity of the intestinal musculature. In addition, this tract is supplied by both sympathetic and parasympathetic fibers which are in turn influenced centrally. The situation is further complicated by the evidence that there are apparently both inhibitory and excitatory fibers in each of the two autonomic systems and these are distributed in different proportions to different areas of the intestinal tract. This means, then, that the response elicited from a given stimulus depends upon the tonic state of the various components at the time the stimulus is applied. Another fact to consider is that the effect of a given agent or stimulus may affect only a part of this system, or different parts in diverse manners, or may possess threshold effects to different degrees on structures of this complex.

Krueger (5) mentions that constipation was recorded as a sequelae a few years after morphine was isolated. Legras (1823) (9) reported an effective cure of persistent diarrhea with about 15 mgm.

of morphine in a syrup. In 1836, G. G. Sigmond (10) mentioned that narcotics "impede the digestive organs and prevent the sensation of hunger; hence the (perverted) use of opium by those who are incapable of purchasing sufficient food. Sometimes they (viz., narcotics) obstruct chymification going forward, if taken during a meal the aliment is sometimes rejected, without having undergone the usual change. Some of them produce constipation, and the large intestines become sluggish, and incapable of obeying the usual stimulus; they lose their habitual power of contractions, and the largest doses of active medicines which should stimulate them to expel their contents are unavailing." Subsequently, a great many studies were undertaken to explain the gastrointestinal effects of morphine.

B. Techniques Used for Study of Constipative Effects of Morphine.

(1). Development of Techniques and Methods for Study.

The first method used was direct observation in the human of the effects of opiates on the herniated intestinal loop, on fistulae, by exposure by laparotomy and on isolated segments. Magnus (1906) (11) first produced a diarrhea in caged cats by a milk diet and then constipation by the administration of 40 to 50 mgm. morphine.

The X-ray technique of Cannon (1898 and 1902) (12,13) greatly increased the opportunity for the study of intestinal motility. Magnus (1903) (14) used this technique on cats and demonstrated

gastric delay with morphine. In humans given 10 mgm. morphine subcutaneously, von den Velden (1909) (15) noted constriction of the pyloric sphincter and the marked delay in stomach emptying time.

The balloon technique, first used by Legros and Onimus (cited by Krueger, (5)) in 1869, showed that 80 mg. of morphine given to a dog with an intestinal fistula decreased the frequency of contractions. Pal, 1900 (citation by Plant and Miller, (16)) using curarized dogs, and balloon recording devices found that denervating the intestine did not alter the intestinal response to morphine.

Uhlmann and Abelin, 1920 (citation by Plant and Miller, (16)) using anesthetized rabbits and guinea pigs, tied cannulas into each end of a segment of small intestine which was connected to a reservoir of Tyrode's solution. Changes in the volume of fluid indicated the contractions of the segment. They reported that low doses of opium decreased both tone and peristalsis while high doses increased tone and contractions.

Plant and Miller (1926) (16) using Thiry-Vella loop dogs with recording balloons showed that tone increased with an increase in dose while atropine had no effect on the morphine intestinal response. Epinephrine, on the contrary, given after morphine was found to relax the intestine for brief periods. But in a denervated preparation the normally minimal effective dose of morphine (0.12 mgm/kgm.) used was found to produce maximal increase in tone while atropine again had no effect.

Gruber, Byrom and Richardson (1932) (17) showed that the decreased tonus and increased peristalsis of a cathartic were quickly reversed by morphine. Toxic cathartics often caused death because morphine allowed time for the absorption and systemic distribution of the cathartic.

Krueger, Howes and Gay (1935) (18) using Krueger's isobaric technique (19) on Thiry-Vella fistula dogs found the lowest dose of morphine and other opiates giving a recognizable response caused a decrease in intestinal tone and peristalsis. This work clearly resolved the conflicting data as to the tonus effect of morphine on the gut.

In 1936, Abbott and Pendergross (20), combined the Miller-Abbott (21) balloon technique for humans with roentgenological studies in order to resolve the variances in interpreting the two techniques. Their idea was that in all hollow viscera the normal movement of contents depends on reciprocal contraction and relaxation, a dominance of either phase impeding progress. They showed that the delayed gastric emptying time was due to duodenal spasm instead of pylorospasm. The duodenum was very sensitive to morphine and constricted tightly within two minutes after the drug was injected. This hyperactivity was followed by subnormal activity which persisted for as long as 24 hours. In their opinion, the chief cause of constipation might be this long period of subnormal activity which was present in the entire intestinal tract.

In checking the so called "peristaltic waves" and "tonus waves", Abbott and Pendergross found that forward movement of the barium meal

could be seen under conditions which did not always correspond to the standard interpretation of the balloon records. While there was a very high correlation with the standard interpretations, the balloons could not be relied upon to measure peristalsis. They also showed that adrenalin in a normal animal caused constriction of the pyloric sphincter but after morphine it caused relaxation. This is in accordance with the observations that epinephrine is inhibitory to contracted intestinal musculature and stimulatory to the atonic or relaxed bowel.

Le Heux and de Kleyn (1932) (22) reviewed the work of Kremer and of Spiegel and Demetriades which concerned the effect of caloric stimulation of the labyrinth on the intestinal tract. In an attempt to evaluate this effect they extirpated the labyrinths of cats and observed the intestinal activity by Cannon's X-ray technique. Stomach emptying time and intestinal motility were markedly reduced. They also reported that the central constricting spasm of the stomach, which had been reported by Magnus (22) to be a property of morphine, was usually observed in these labyrinth-free animals. Ingelfinger and Moss (1942) (23) also demonstrated by Miller-Abbott balloons in humans that an immediate and generalized contraction of the duodenum could be elicited by caloric stimulation of the labyrinth or after the administration of morphine. This contraction apparently did not involve the pyloric sphincter because the constricting duodenum would readily push the balloon past the pyloric sphincter back into the stomach.

Loomis (1948) (24) found that morphine stimulated the circular muscles of the duodenum, but relaxed the longitudinal muscles. The presence of physostigmine or atropine did not change the intestinal

response to morphine.

The statements usually found in the text books concerning the action of morphine are in general confusing with such statements as: "The tone and motility of the small intestine are increased by morphine. The passage of the food bolus is delayed (25)". In an attempt to answer this problem, Vaughan Williams and Streeten (1951) (26) used special Thiry-Vella loop dogs (27) to measure the ability of the intestine to transport water against pressure. By means of this very sensitive procedure, they demonstrated the shortcomings of balloon and hard bolus procedures and resolved the apparent discrepancies of interpretation of such data.

As demonstrated by Vaughan Williams and Streeten, a primary factor to be considered in morphine constipation is the closed lumen which requires pressure to distend it. When the gut assumes the sausage appearance, a characteristic morphine effect, the distended muscle fibers cannot exert enough coordinated pressure to push a soft bolus beyond the constriction. All previous work had demonstrated the speed-up of intestinal activity immediately and during the first hour after morphine by noting the progression of hard rubber balls, metal spheres, turgid balloons, and other solid materials. The formed faecal mass contained in the colon likewise is promptly eliminated after administration of morphine. These observations gave rise to the erroneous belief that morphine stimulated intestinal motility in contrast to the observable fact that the patients became constipated. Other workers had mentioned but did not fully appreciate the observation that considerable force was required to push a hard bolus into a fistulae after morphine. Thus, the

manual, forceful insertion of a rubber ball bolus into the morphinized animal had the advantage of an artificially produced initial higher energy level. Such a condition could not be duplicated naturally in an intact animal except in the colon.

The explanation for the initial increased speed of propulsion of a hard bolus or ball resides in the increased tonus of the tract and in the ability of the contracting fibers (and residual peristaltic activity) to push a hard bolus against the closed lumen to force it open. Since this is not possible with a soft bolus which is normal for the intestinal contents, constipation is the result.

Vaughan Williams and Streeten point out that for transportation of fluid, a closed intestinal lumen must be assumed which is progressively maintained while traversing the segment. Too much pressure will prevent the lumen from closing, too great a closing force will prevent it from opening; if peristaltic progression is diminished, the propulsion of material will be reduced or stopped. In a few instances where other workers had continued their experiments for longer than an hour, it was found that the bolus moved much slower than normally. However, this observation was neither explained nor explored. This important observation will be considered later.

Streeten (1950) (28) has shown that sodium chloride lack will decrease intestinal motility. As the concentration is decreased, the peristaltic movements are the first to drop out. Acetylcholine, physostigmine, and neostigmine are ineffective in sodium chloride lack but tetra ethyl ammonium bromide is effective, perhaps due to its ability to substitute for the Na ion. Streeten also resolved the

conflicting data concerning the atropine reversal of the morphine effect. At doses of morphine below 0.32 mgm./kgm. the atropine would reverse the effect but above this dose there was no reversal, as is generally reported by most research groups. Considering their *in vitro* morphine effects, they explained this as the effect of low doses on the cholinergic mechanisms, which atropine will reverse, and the direct muscle component which atropine will not counteract.

The mechanism of constipation now being conveniently divided into the two components, neurotropic, and musculotropic, the problem then is to find an analgesic which will not produce the intestinal effects, or a corrective drug to counteract this effect. This paper will then attempt to compare the intestinal activity of the newer synthetic analgesics with the standard drug, morphine, to evaluate the currently used testing methods, and to provide control data for future comparison in the determination of the effects of other drugs which can be administered with morphine, its derivatives, or its substitutes. It is thereby hoped that the road to effective analgesia without constipation may be made a little less remote.

(2). The Excised intestinal method of measuring in vivo drug effects.

According to Macht and Barba-Gose (1931) (29), the terminal excision and measurement for intestinal propulsion studies in the intact animal (mice) was first used in Germany. They cited Laqueur, 1914, Fuhner, 1925 (30); and Loewe and Faure, 1925 (31). The last mentioned authors tested laxatives with india ink as a marker, but stated that it was not too satisfactory and suggested the use of finely divided carbon. Following this advice, Macht and Barba-Gose used carbon black suspended in a gum tragacanth carrier in the study of the laxative effect of Ruvettus oil and Macht (32) later, higher alcohols in rats. The index used was the percentage of the distance that the carbon black traversed from the pylorus to the rectum in 50 minutes. Emerson (1933) (33) used the Macht technique on rats to test the laxative principle in prunes. He used gum tragacanth and charcoal; his time interval was 50 minutes.

Patterson, Smith and Hale (1938) (34) studied the intestinal response of rats to CO. Using food containing Fe_2O_3 as a marker, they compared the distance traversed by the carbon meal in a 40 minute period and found a 33% slowing when compared with a control group. They substantiated this claim by measuring the evacuation time which was 22% prolonged over the normal. They pictured a very ingenious excrementometer with which they worked. Smith and Penrod (1941) (35) used both these methods to demonstrate the diminished motility produced by amphetamine except that they used a time interval of 30 minutes and

expressed the distance as percentage of total length.

Van Liere, Stickney, Northrup and other workers have used a modification of Macht's technique as a method to compare the effect of a great number of agents on intestinal motility (36-45). They used 10% carbon black and 10% gum acacia preparation administered by stomach tube. For dogs the time interval was usually 30 minutes, for rats 40 minutes; but, always comparing with a control, they used different time intervals as the experiments warranted. Because they had noticed continued intestinal movement in animals killed by a blow on the head, they sacrificed many of their rats by using ether which they believed assured stoppage of movement in the intestinal tract. They demonstrated that the intestinal contents moved faster in the upper part of the small intestine than the lower and showed that the rat and dog were comparable as test animals. While the material moved faster in the intestinal tract of an adult than in the pup, and the correlation between the speed of movement and intestinal length was not always apparent, the percentage of distance traveled by the meal in the total intestine was the most accurate and reproducable method of comparison. In general, the material moved faster, the longer the intestines. Because of the pyloric effect, they suggested that the material be placed in the duodenum, if possible, further mentioning that administration into the duodenum by present techniques would cause undue reaction. Since 1944, these workers have shown that ergotamine and prostigmine increase intestinal motility, while atropine, Banthine, Bentyl, T.S.A., Ephedrine, Amphetamine, ether, CO_2, and anoxic

anoxia, to which they later demonstrated some acclimatization, decreased motility while cocaine had little effect in the intestinal tract.

Karr (46) in 1947, in this department used Macht's method, but selected 60 minutes as the time interval. His procedure has been followed in this study to verify technique.

The Merrell Research group described the testing of spasmolytic drugs by the Macht method in 1950 (47). They used a 30 minute time interval and measured the per cent distance traveled in the small intestine only. Their mixture of 5% carbon black and 5% gum tragacanth was found satisfactory in this laboratory.

A recent variation by Holtkamp, Whitehead and Hill (1951) (48) in a study of antihistimes was to feed carmine impregnated briquets to starved rats using the time of appearance of red feces as a measure of intestinal activity. This method involves loss trauma to the rat.

(3). The Rabbit Pellet Method of Measuring in vivo Drug Effects.

In order to evaluate the constipating effect of a new series of analgesic drugs which he was then studying, Eddy (49,50) in 1932 devised a method which depended upon the dose required to completely supress intestinal evacuation in each of 10 rabbits for one or more 30 minute periods for several hours after injection. Eddy, by this procedure, found the minimal effective dose for morphine to be 6 mgm./kgm. He further demonstrated that general depression alone did not produce this effect as evidenced by the administration of urethane and several barbituric acid derivatives which failed to produce constipation.

Emerson (33) using Eddy's technique to measure the laxative effects of prune extracts found that the percentage of rabbits defecating in the allotted periods was increased by these prune extracts. Their control average was such that only about one-third of the rabbits defecated in the period of time measured. As this was considerably less than Eddy's control value, they advanced the explanation that the diet was different.

Sato (1936) (51) modified Eddy's method and showed that constipating drugs would statistically reduce the number of scybala passed by the rabbit each hour from 9:00 AM to 4:00 PM. His minimal effective dose for morphine might be 1 mgm./kgm., but more data should be presented to determine this. Krueger's (5) tabulation of these results would show 2 mgm./kgm. to be the minimal effective dose. The pellet count regularly ranged between 40 and 56 for the 7 hour period of observation. Eddy's observations that urethane had no constipating effect were substantiated. However, in animals which had been sympathectomized, Sato found that morphine exhibited little effect on scybala passing and his dose range was 5 to 20 mgm./kgm.

Karr in his studies on methadone (Dolophine(R)) and meperidine (Demerol(R)) in this laboratory in 1947 used Eddy's method to study constipation effects.

Scott, et al (1947) (52), used this method, among others, in their comparisons of intestinal effect of morphine.

The method of feeding carmine inpregnated briquets used by Holtkamp, et al (48) in their study on rats might easily be applied to rabbits.

EXPERIMENTAL

In this study, an attempt has been made to compare the synthetic analgesics with morphine. A preliminary check of the LD_{50} value of L-isomethadone hydrochloride and N-allyl-normorphine (Nalline(R)) was first done. The comparison of the effect of the drugs on intestinal motility has been undertaken by means of Macht's method of excised intestine measurement in the rat and the Eddy method of measuring changes in rabbit scybala production.

I. Toxicity Studies on Analgesic Drugs Used.

A. In order to check the dose ranges used in this study, a few of the several analgesic drugs to be investigated were selected for determination of their LD_{50}. Since our main interest was in L-isomethadone and Nalline(R), toxicity studies were done first on these drugs.

L-isomethadone has been reported by Jenny & Pfeiffer (1948) (53) to have an LD_{50} value of 25 mgm./kgm. when administered intraperitoneally to a mouse. Winter and Flataker (1950) (54), using subcutaneous injections, found the LD_{50} to be 21 mgm./kgm. in the mouse. On the basis of this data a preliminary group of 20 mice was given a dose of 30 mgm./kgm. intraperitoneally and no deaths occurred. Further experimentation roughly placed the LD_{50} for our group of white mice given L-isomethadone to be in the neighborhood of 60 mgm./kgm. This is considerably higher than that of the authors previously mentioned. The results of intraperitoneally

injected mice with L-isomethadone were as follows:

Dose mgm./kgm.	No. rats	No. deaths
30	20	0
45	20	3
60	20	12
75	20	12
90	20	20

It is of interest to note that when the time of death of the mice in the LD_{50} experiment is plotted on a graph, the curve assumes a biphasic character which calls to mind the biphasic intestinal motility curve (Graph 1, Page 25).

B. N-allyl-normorphine (Nalline (R))

Unna (1943) (55) reported the LD_{50} of Nalline to be 670 mgm./kgm. and Morphine Sulphate 660 mgm./kgm. when administered subcutaneously. All Nalline deaths were due to respiratory failure because the hearts were still beating terminally. Death was always within 15 to 90 minutes, as contrasted with morphine, where deaths were within 45 minutes to 3 hours.

Hart & McCawley (1944) (56) substantiated these findings for Nalline when they reported the subcutaneous LD_{50} to be 700 mgm./kgm. They also reported that intraperitoneal injections produced an LD_{50} value of 491 mgm./kgm.

In a preliminary testing of Nalline by intraperitoneal injection of white mice, the results in this laboratory would tend to place the LD_{50} value slightly over 600 mgm./kgm. Most deaths occurred within 4 minutes to 15 minutes. The time of death curve appears to be hyperbolic and the point of survival is near the critical point of the curve. This is somewhat like the L-isomethadon curve except that

the second phase is missing.

We also investigated the antidotal effects of Nalline on L-isomethadone toxicity, since recent work has indicated that Nalline effectively reverses the respiratory depressant action and other toxic effects of narcotic agents. We found that when Nalline(R) is administered at an equal dose with L-isomethadone at a dose level of 90 mgm./kgm., the first part of the biphasic curve shown in graph 1 appears to be potentiated, while the second part is inhibited. This dose level of Nalline is well below its own LD_{50} value of about 600 mgm./kgm.; we have observed no Nalline deaths below 400 mgm./kgm. in our limited series.

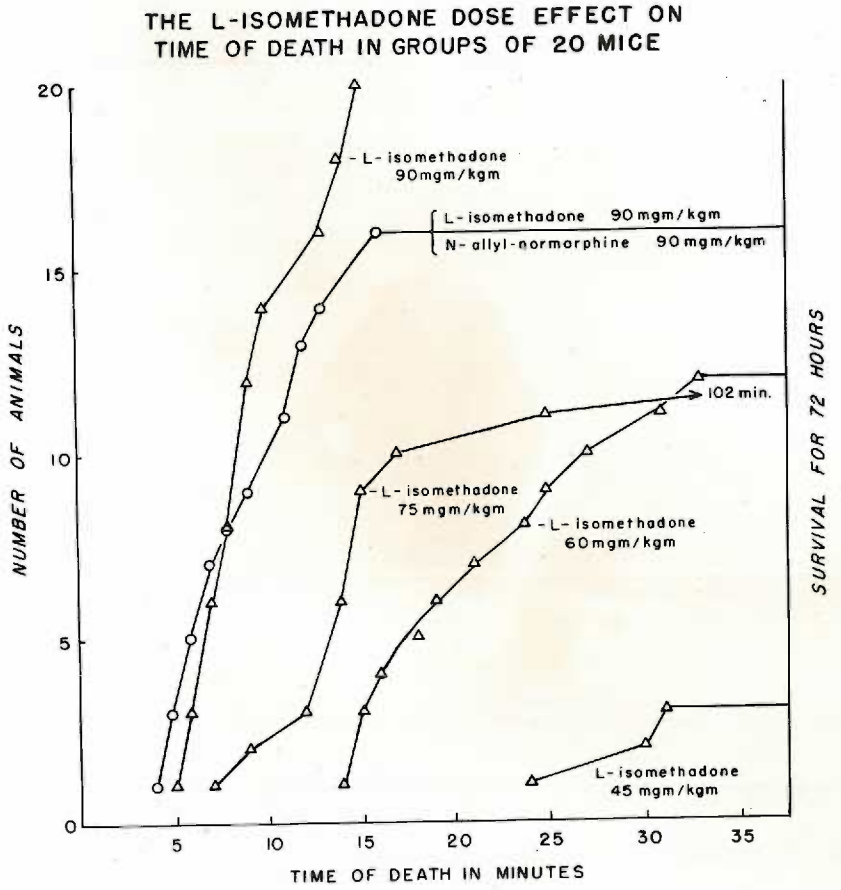
II. A Study of the Effects of Various Analgesics on the Intestinal Motility in the Rat Using Macht's Method.

A. Procedure.

1. Animals:

The Sprague-Dawley strain, albino rats, were used in most of these studies. They were chiefly unused, excess-breeder animals from the Department of Biochemistry (Medical School), or discarded rats used in other experiments. All rats had a rest period of three weeks or more to recover from any effects of drugs previously administered.

The Wistar rats were unused, excess stock animals obtained from the colony at the Biochemistry Department at Oregon State College. Because of some apparent differences, the different strains will be considered separately.



Graph 1. The time of death for mice administered various doses of l-isomethadone. All animals (except one at 102 minutes) which lived beyond 35 minutes survived until the experiment was terminated 72 hours later.

2. Charcoal Meal:

This consisted of a partly fluid paste of tragacanth to which animal charcoal was added by careful and thorough mixing in a mortar. The material was made thin enough to be used in a 10 cc. hypodermic syringe. Usually a 5% carbon black and 5% tragacanth mixture was found satisfactory.

3. Intubation:

Administration was made in the unanesthetized rat held in the left hand by using a solder-tipped, curved needle rather than a catheter. Approximately 1.0 cc. of the charcoal mixture was instilled. The animals were in a fasting condition before use.

4. Controls:

With each group of rats used, a number of animals served as controls. This was essential to the experiment since those animals served for obtaining data for the length and percentage of intestine traversed under the conditions of the particular charcoal-tragacanth suspension used, room temperature, atmospheric pressure and other conditions. As nearly as possible, animals for controls were selected at random from the selection available at the time.

5. Drugs:

The various analgesics were injected subcutaneously between the scapulae in the doses listed in Table I. Usually the dose was calculated to be contained in a solution which could be converted directly from two times the weight of the animal to the calibration in hundredths of a cc. on a tuberculin syringe. A similar amount of saline was administered to the animals receiving placebos. The volume of the solution was 2 cc./kg.

The drug was given one-half hour before intubation of the charcoal meal.

Doses used approximately equalled the dose which would increase analgesia 100% as previously estimated in this laboratory (Semler and David)(57) or else where for the rat. The dose range was later extended extensively in order to explain the "pylorospasms" obtained with some drugs, and to make a comparison of dose relationship to effect of drug.

6. Estimation of Length of Intestines the Charcoal Meal Traversed:

One and one-half hour after saline or drug injection and one hour after charcoal meal, the animal was killed by a blow on the head. The intestines were then excised and stripped of omental attachments so that they could be laid out on a piece of paper towel. The total length of intestine (from pylorus to anus) was measured, then the distance the charcoal meal had traversed was measured. The distance traveled by the charcoal was then expressed as a percentage of the total length. All comparisons will be made on the basis of this percentage figure.

7. Method of Sacrifice:

Van Liere's group mentioned that ether, because it "immediately" stopped intestinal motility, was used to kill the animal. A series of animals was dropped into a bell jar saturated with ether vapor and the average time required to produce "sleep" was two minutes (119 seconds).

Considering the fact that in 2 minutes and 22 seconds (S.D. $\pm$ 12 seconds) a rat could be sacrificed by a blow on the head, the

intestines removed, cleaned of mesenteries, and measured, the error produced by such activity was considered insignificant. As soon as the intestine is removed from the body cavity, it cools rapidly; just a few degrees and all motility ceases. Omission of the ether procedure saves two minutes.

III. Results of Study of Effect of Analgesics on Per Cent Distance Traversed by Charcoal Meal in the Rat's Intestine (Macht's Method).

A. Presentation of Tables and Figures Showing Results.

The results, expressed in percentage of the total length of the intestines traversed by the charcoal meal when different drugs or the saline placebos were administered are graphically shown in a number of figures and accompanying tables. These data are presented in such fashion herewith; a brief discussion of significant results and pertinent comments follow.

Figure 1 shows the relationship of the dose used to the percentage distance of the intestinal tract traversed by the carbon meal for the several analgesic drugs studied. Only one point is shown on this figure for the following drugs since it was not in the scope of this study to establish curves for all the drugs: meperidine hydrochloride, dl-isomethadone, dl-methadone and l-methadone. An examination of the curve shows that l-isomethadone has a biphasic action on the intestinal tract while morphine and Nalline show a more progressive response effect to increased dosage. This biphasic action is apparent for another analgesic used in this study, dl-alpha acetylmethadol. The curves also show that l-isomethadone at

doses below 2 mgm./kgm. is less constipating than morphine, but at higher doses this drug is considerably more constipating. At comparable analgesic doses for rats, as determined by other workers (57) in this laboratory, it is seen that dl-alpha acetylmethadol is less constipating than morphine. However, when considered on an equivalent mgm./kgm. dosage basis, then dl-alpha acetylmethadol is found to be more constipating than morphine.

The data used for constructing the graphs in Figure 1 is listed in Table 1. Table 5 is a supplementary tabulation which may be considered at this time since it has been included in order to compare the data for several drugs we studied with the data obtained previously in this laboratory for the same drugs and dosages by Karr in 1947. The very close correlation of these data, obtained by different workers at different times, indicate the practicability of Macht's technique for this type of investigation.

In many instances following drug administration, but never when only saline was injected, it was observed on exposing the intestinal tract in the rat that the carbon meal had failed to pass the pylorus and was still retained within the stomach. This phenomenon has been called, for convenience, "pylorospasm" which condition, as part of the drug action in the rat, it probably is.

Table 2 and Figure 2 shows the number of animals, expressed as percentage of the number studied for a given drug and dosage, which showed "pylorospasm" at the end of the observation period. That there is a parallel relationship of the percentage of pylorospasms encountered to the dose administered is apparent in the graphs of

Figure 2. Demerol(R) and Nalline(R) are plotted at multiples of ten times the abscissal doses because they appear to fit the graph as one-tenth strength compounds.

Of incidental but somewhat pertinent interest in this study comparing the constipative effects of a number of new analgesic compounds, is the supplementary investigation made of the antagonistic effects of N-allyl-normorphine (Nalline(R)) to the gastro-intestinal activity of l-isomethadone and dl-alph acetylmethadol. The results of this preliminary experiment are shown in Table 3 and Figure 3. The graph shows the antagonistic effect of Nalline(R) when administered at several dose ranges (abscissa) to the percentage distance traversed and the percentage of pylorospasms (ordinates) when 4 mgm./kgm. of l-isomethadone or dl-alpha acetylmethadol were employed. It is apparent that Nalline(R) considerably offsets the "constipating" effects of these two drugs since, under its influence, the distance the carbon meal moves in an hour is increased and the incidence of pylorospasm reduced. That this increase in the percentage distance traversed by the carbon meal when Nalline(R) is given along with an analgesic drug is an actual one and not an artifact of the data calculations is substantiated by the fact that animals showing pylorospasm were not included in the percentage-distance-traversed determinations. The data in Table 3 and Figure 3 further suggest that the activity of dl-alpha acetylmethadol is counteracted more effectively by Nalline(R) than are the effects of l-isomethadone, in the doses used, on the intestinal tract.

Table 4 shows the data obtained for Wistar strain rats with a comparison for similar data with Sprague-Dawley rats. For Nalline(R), some divergence of effect appears.

TABLE 1

THE MEAN PERCENTAGE INTESTINAL LENGTH TRAVERSED BY A CHARCOAL MEAL IN THE RAT'S INTESTINE FOLLOWING INJECTION OF CERTAIN ANALGESIC COMPOUNDS

DRUG	DOSE	NO. OF RATS	MEAN PERCENTAGE INTESTINAL DIST. TRAVERSED BY MEAL	STANDARD ERROR	STANDARD DEVIATION
	mg./kgm.		%		
Controls (no drug)	-	25	64.6%	1.3	6.3
Controls, Saline	2 cc./kg.	140	63.9	0.8	9.9
Total Controls		165	64.0	0.7	9.5
Morphine Sulfate	1	19	39.4	3.0	13.5
" "	2	32	30.1	2.6	13.6
" "	4	13	23.6	2.6	9.3
" "	6	22	17.4	1.8	8.8
" "	8	11	13.5	1.8	6.2
" "	10	9	5.8	1.5	4.5
Meperidine HCL	20	19	56.9	3.2	13.9
dl-methadone HCL	2	18	45.0	3.8	16.1
l-methadone HCL	2	20	17.4	2.5	11.4
dl-isomethadone HCL	2	20	55.8	2.5	11.5
l-isomethadone HCL	1	36	51.1	2.2	13.3
	2	40	42.7	2.7	17.2
	3	14	6.3	1.6	6.1
	4	7	8.9	2.7	7.2
	6	2	3.3	-	-
N-allyl-normorphine	2	19	54.7	2.4	10.5
	10	15	57.1	3.9	15.2
	20	10	36.9	5.0	15.9
	40	11	30.5	4.1	13.5
	80	10	14.6	5.2	16.6
	120	7	2.3	0.5	1.43
	160	2	0		
Alpha Acetylmethadol HCL	1	23	24.0	1.6	7.8
	2	34	28.3	2.3	13.6
	4	10	10.2	4.8	15.3
	6	3	3.3	0.4	0.7
Heptasone HCL	1	9	62.1	6.6	19.8
	2	14	47.7	4.5	16.9
	4	4	51.4	8.1	16.3

TABLE 2

NUMBER AND PER CENT OF ANIMALS ADMINISTERED CHARCOAL MEAL AND GIVEN CERTAIN ANALGESIC COMPOUNDS WHICH SHOWED RETENTION OF MEAL IN STOMACH ("PYLOROSPASM")

DRUG	DOSE mg./kg.	TOTAL NO. OF RATS	ANIMALS SHOWING RETENTION OF CHARCOAL MEAL NO.	%
Controls (no drug)	-	25	0	0
Controls (Saline)	1.0 cc.	74	0	0
Morphine Sulfate	1	19	0	0
	2	43	11	25.6
	4	14	1	7.1
	6	26	4	15.4
	8	12	1	8.3
	12	12	3	25.0
Meperidine HCL	20	20	1	5.0
dl-Methadone HCL	2	22	4	18.0
l-Methadone HCL	2	26	6	23.0
dl-isomethadone HCL	2	21	1	5.0
l-isomethadone HCL	1	37	1	2.7
	2	42	2	4.7
	3	23	9	28.1
	4	21	14	66.6
	6	14	12	85.6
N-allylnormorphine HCL	2	19	0	0
	10	15	0	0
	20	10	0	0
	40	11	0	0
	80	10	0	0
	120	10	3	30
	160	2	2	100
Alpha Acetylmethadol HCL	1	24	1	4.2
	2	38	4	10.5
	4	32	22	68.8
	6	11	8	72.0
Heptazone HCL	1	9	0	0
	2	18	4	22.0
	4	10	6	60.0

TABLE 3

THE ANTAGONISTIC ACTION OF N-ALLYL-NOR-MORPHINE TO THE EFFECTS OF ANALGESIC DRUGS ON THE INTESTINAL MOTILITY

DRUG	DOSE mgm./kgm.	NALLINE (R) DOSE mgm./kgm.	NO. RATS	STRAIN OF RAT	% DIST. TRAVERSED	S.D.	S.E.	PER CENT PYLOROSPASM
A Acetylmethadol	4	0	10	S-D	10.2	15.3	4.8	68
" "	4	4	18	S-D	47.8	14.2	3.3	10
" "	4	8	5	W	45.1	7.9	2.2	37.5
" "	4	8	7	S-D	41.5	14.0	5.4	30
" "	4	20	9	S-D	44.2	18.7	6.2	0
" "	4	40	11	S-D	49.6	7.3	2.2	0
l-isomethadone	4	0	7	S-D	8.9	7.2	2.7	63
" "	4	2	6	S-D	26.6	14.5	6.0	40
" "	4	4	13	S-D	26.3	17.5	4.8	35
" "	4	8	5	S-D	34.5	13.9	6.2	50
Nalline (R) Acetylmethadol	8) 4)	*	5	W	32.9	21.6	9.7	16.6
Nalline (R) Acetylmethadol	4) 4)	**	10	W	42.7	11.4	3.6	0

Nalline was administered at the same time the carbon meal was intubated ($\frac{1}{2}$ hour after analgesic).

* Sequence here was (1) Nalline, (2) $\frac{1}{2}$ hour later AAM, (3) $\frac{1}{2}$ hour later carbon meal.

** Nalline and AM were in the same solution, therefore administered together.

TABLE 4

COMPARISON OF EFFECTS OF CERTAIN ANALGESIC DRUGS ON THE MEAN PERCENTAGE INTESTINAL LENGTH TRAVERSED BY A CHARCOAL MEAL IN THE INTESTINE OF THE SPRAGUE-DAWLEY AND THE WISTAR STRAIN OF RAT

		SPRAGUE-DAWLEY STRAIN				WISTAR STRAIN					
DRUG	DOSE	NO. OF RATS	MEAN % DISTANCE TRAVERSED	S.D.	S.E.	NO. OF RATS	MEAN % DISTANCE TRAVERSED	S.D.	S.E.	NO. SHOWING PYLORO-SPASM	% PYLORO-SPASM
	mg./kg.										
(Controls) Saline	1.0 cc.	140	64.0	9.5	0.7	44	61.2	11.0	1.6	0	0
Morphine Sulfate	2	32	30.1	13.6	2.6	12	28.9	10.21	2.9	0	0
l-isomethadone HCL	2	40	42.7	17.2	2.7	23	27.6	14.2	3.0	1	4.2
Alpha Acetylmethadol HCL	2	34	28.3	13.6	2.3	22	23.6	29.37	6.2	6	21.4
	4	10	10.2	15.3	4.8	7	10.9	18.0	6.8	3	30.0
N-Allyl-Normorphine HCL	2	19	54.7	10.5	2.4	-	-	-	-	-	-
	4	-	-	-	-	9	34.1	15.0	5.0	1	10.0
	10	15	57.1	15.2	3.9	19	34.0	19.1	4.3*	0	0

* "T" value 3.8; probability significance level greater than 0.005.

TABLE 5

THE REPRODUCIBILITY OF RESULTS USING MACHT'S TECHNIQUE

DRUG	DOSE mgm./kgm.	% DIST. TRAV. VAN ARSDEL	% DIST. TRAV. KARR	S.E. VAN ARSDEL	S.E. KARR
Controls	-	64.0	66.1	0.7	± 1.6
Morphine SO_4	2	30.1	-	2.6	-
Morphine SO_4	*	-	23.6	-	± 3.4
Morphine SO_4	4	23.6	-	2.6	-
Meperidine HCL	20	56.9	56.7	4.3	± 4.6
Dolophine	2	45.0	45.9	3.8	± 2.6

* Not stated in paper; presumed to be 2 mgm./kgm.

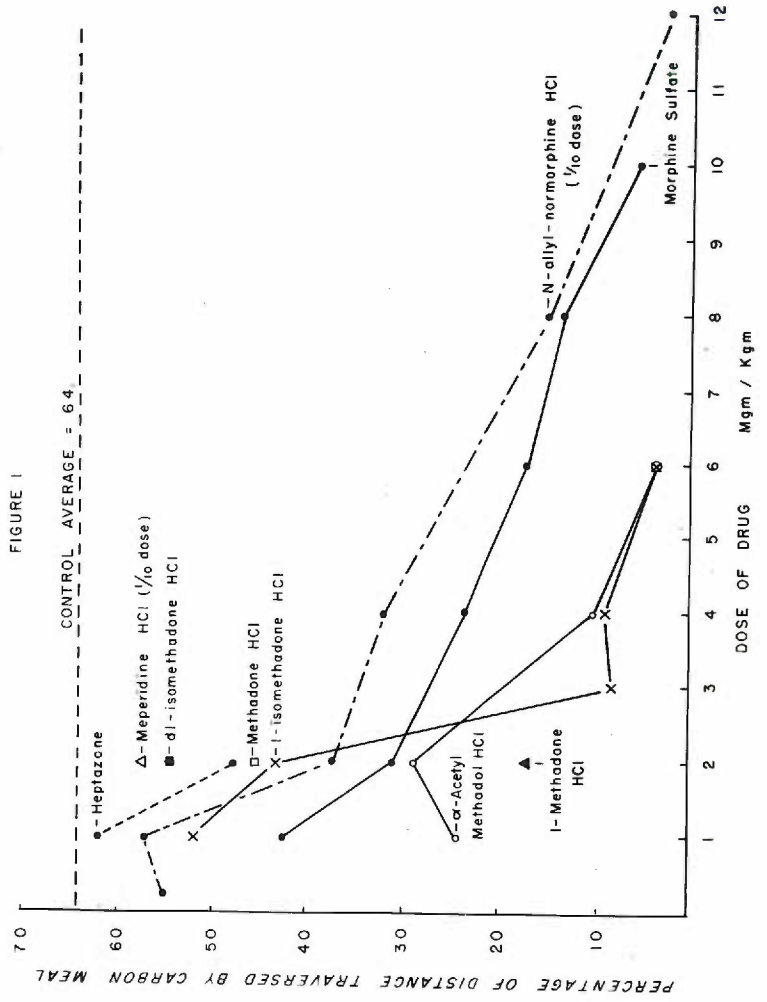


Figure 1. The relationship of the dose used to the percentage distance of the intestinal tract traversed by the carbon meal for the analgesic drugs studied and in comparison with the control.

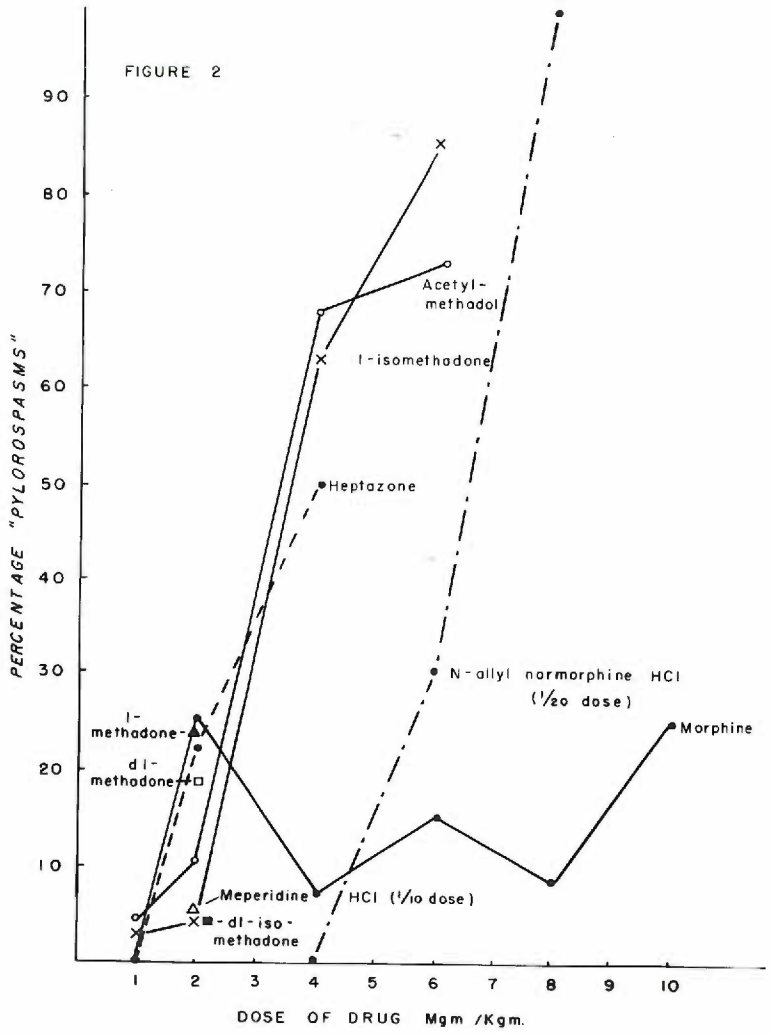


Figure 2. The number of rats, expressed as percentage of the number studied for a given drug and dosage, which showed "pylorospasm" at the end of the observation period.

Fig. 3

THE DOSE RELATIONSHIP OF NALLINE ANTAGONISM
TO 4 mgm/Kgm OF TWO SYNTHETIC ANALGESICS

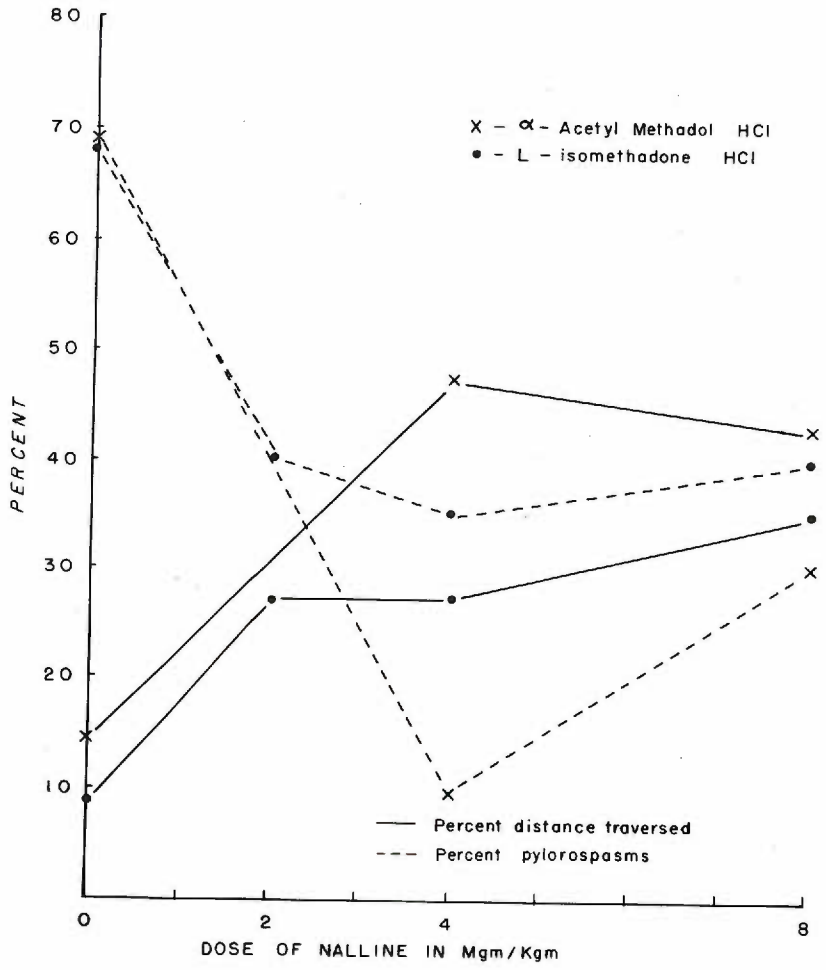


Figure 3. The antagonistic effect of Nalline(R), at several dose ranges, to the constipating effect of 4 mgm./kgm. of alpha acetyl methadol and l-isomethadone when measured in rats.

B. A Comment on The Phenomenon of Pylorospasm Encountered in Rats When Administered Certain Analgesic Drugs.

During the early experiments performed with Macht's method using standard analgesic drugs such as morphine and meperidine, the charcoal meal failed to pass from the stomach into the intestines in some rats. This effect has been considered as "pylorospasm". Northrup, Stickney and Van Liere (1952) (37) must have had this same experience since they mentioned that those animals were discarded where the meal failed to progress 10% of the distance of the intestinal tract.

This condition of "pylorospasm" might possibly be explained on the basis of trauma to the animal incurred during intubation with the curved injecting needle; however, since no animals used as controls ever showed pylorospasm and narcotized animals were much easier to intubate, this was considered as a drug effect. After using several dose ranges of the different analgesics, it soon became apparent that there was a direct dose relationship to this aspect of drug effect, as can be seen in Figure 2.

Increasing dosage of the drugs produces an increase in the percentage of animals retaining food in the stomach. Apparently morphine is the exception to the rule. This may be an artifact of interpretation. At high doses of morphine, the pyloric and upper duodenal area is so tightly constricted that it is blanched. In many cases, the "color" had passed the pylorus but the volume of contents was not normal. Most of the data had been gathered before this difference was appreciated. Gruber, et al, (58) noticed that the

duodenum contracted forcefully within 2 minutes of injection, then after a period of extreme spasm, was hypotonic for long periods. Perhaps this effect, or the anoxia produced by the blanching, could produce intermittent relapses of the muscle tonus to allow the carbon to pass into the duodenum. Also, while not investigated in this study, there is also the possibility that higher doses of the other analgesic drugs might have produced this same effect.

The dose of 2 mgm./kgm. was selected for several of these analgesics because it allows comparison with the analgesic effectiveness of these agents which, at this dosage, show a 100% threshold increase in activity. As determined by Herbert Semler in this laboratory, the comparable analgesic effects for some of the drugs when expressed as percentage increase in pain threshold determined by the D'Amour-Smith technique are as follows:

Drug	Dose mgm./kgm.	Per cent increase in "pain" threshold
Morphine Sulfate	4	50
	6	100
dl-alpha acetyl-methadol	1	45
	3	125
l-isomethadone	1	-
	2	120

While it can be readily seen on the basis of the above data (Figure 2) that a comparable analgesic dose of morphine (4 or 6 mgm./kgm.) produces greater intestinal side effects, we have compared, for convenience, the intestinal effect of 2 mgm./kgm. of the analgesics (or their ten fold multiples, as used for Nalline(R) or meperidine).

Morphine at 2 mgm./kgm. caused the highest incidence of pylorospasm (25.6%) followed by l-methadone (23%) and heptazone (22%) with the lowest incidence being for meperidine (5%), dl-isomethadone (5%) and l-isomethadone (4.7%). Nalline at 20 mgm./kgm. showed no pylorospasms. Apparently, this effect is related to the other analgesics as a 1/40 strength effect since the one-twentieth dose curve can be moved over to coincide with the other curves at the one-fortieth position.

C. Per Cent Intestine Traversed. - Table 1 presents this data. This information was obtained by excluding those rats which showed pylorospasm since the charcoal meal did not enter the intestinal tract and no measurement could be made. The statistical standard deviation and standard error are also shown. The results obtained for each group of rats are considered separately.

1. Control Rats Administered Saline. - The first 25 "control" animals were not injected with a saline placebo. Such an omission appears to have a minimal effect, because when these results are compared with those given saline injections (Table 1), very little difference is noted.

All subsequent 140 control animals, studied in small groups at the same time drugs were used, were injected subcutaneously with 2 cc./kg. of a physiological saline solution.

The distance traversed by the carbon black in one hour averaged 64% in all the Sprague-Dawley control animals with a standard error of 0.7. This is assumed to be the normal for rats. Remarkable agreement of this figure with Karr's average of 66.1%, formerly

obtained in this laboratory (Table 5), leads one to accept this as the average mean per cent of the length of the intestine traversed by the charcoal meal in the normal rat one hour after receiving the meal.

There tends to be some drift of the average value due to the rat source, size, time of day, weather conditions and perhaps season. While a comparison of the animal group with its control for that day would change an average value occasionally, still the relative positions of the points on the curve would not be changed. An examination of the following data demonstrates this drift, but even the lowest average is well above drug effect averages. Consequently, all groups have been placed together with the overall average of each drug and dose plotted. (see Table 6)

2. Morphine. - This drug was used as a "reference control" to allow comparison with the other analgesics tested. When several dose levels were used, it was noted that the percentage distance traversed by the charcoal meal varied inversely with the dose, occurring in a linear fashion.

At a dose of 2 mgm./kgm., 32 rats showed a mean distance percentage of 30.1% of gut traversed compared with 64% for the controls, 56.9% for meperidine, 45% for dl-methadone, 55.8% for dl-isomethadone, and 42.7% for l-isomethadone. This suggests that morphine was more constipating than any of these drugs but it was less constipating than l-methadone (17.4%) and slightly less so than dl-alpha acetylmethadol (28.3%) at a dose of 2 mgm./kgm. However, at doses which produce comparable analgesia, morphine

TABLE 6

Placebos - Record of Average Per Cent Distance Traversed in Intestinal Tract in Sprague-Dawley Rats Injected with Saline

Date	No. Rats	Ave. Per cent Dist. Traversed
8/8 - 15/51	25*	64.6
9/13 & 19/51	6	75.4
Date not recorded	5	70.6
10/20/51	3	72.3
11/9/51	5	68.2
12/9/51	7	66.2
1/5/52	8	57.8
2/10/52	6	70.7
3/2/52	8	61.8
5/5/52	8	66.4
5/27/52	9	69.5
6/29/52	9	64.6
9/10/52	10	53.9
9/12/52	5	61.5
9/14/52	8	66.7
10/10/52	5	58.0
10/12/52	7	64.9
11/12/52	6	56.9
11/12/52	8	59.5
11/26/52	6	64.4
11/26/52	4	62.5
12/7/52	7	59.7
2/3/53	6	56.0

* No saline injection.

appears more constipating than all drugs tested. Karr (1947) (46) using presumably the same dose, found that the average for morphine was 23.4%.

Incidental observations made on the rats given morphine show some with constricted pupils, many with dilated pupils, a "Straub-tail reaction" and excitement, provoked by noise or touch, the two latter responses occurring with large doses.

3. Meperidine HCl. - Twenty rats given a dose of 20 mgm./kgm. of meperidine showed an average percentage of gut traversed of 56.9%, (S.E. 4.3%). This corresponded closely to Karr's average of 56.7% (S.E. 4.6%).

4. dl-methadone. - This drug, injected into 18 rats in a dose of 2 mgm./kgm. produced an average percentage distance traversed by the carbon black of 45%, closely comparing with Karr's figure of 45.9% (± 2.6%). Dilatation of pupils and a Straub tail reaction was noted in most rats.

5. l-methadone HCl. - With 2 mgm./kgm. given to 20 rats, the average percentage distance traversed was 17.4%, sigma 11.4. Most of the animals appeared catatonic with a "spread eagle" stance of the hind legs, some lacrimated, and many had dilated pupils. On post mortem handling many rats developed intestinal intussception (may have been present before handling) showing continued activity of the drug after death.

6. dl-isomethadone HCl. - In the 20 rats given this drug at 2 mgm./kgm., one female rat went into convulsions 18 minutes after injection and died 4 minutes later. One other rat appeared "dopey" 30 minutes after injection but this effect was short-lived. All rats in this series had tense abdominal muscles and a "Straub-tail" reaction. Only one animal showed a "pylorospasm". The mean per cent average distance traversed by the meal was 55.8%, sigma 11.5. At autopsy the longitudinal muscles of the intestine appeared to be relaxed.

7. l-isomethadone HCl. - In the group of animals injected with 2 mgm./kgm. of l-isomethadone, differences were noted in three groups (Sprague Dawley Strain) when studied at different times. The mean averages of the percentage distance traversed for these groups were: a. (15 rats)-53.7%; b. (15 rats)-38.7%; c. (10 rats)-32.0%; these 40 rats had the listed average of 42.7%. At the same time the first fifteen Sprague-Dawley rats were studied, 23 animals of the Wistar strain were also given 2 mgm./kgm. of l-isomethadone and an average of 34.6% found; a marked statistical difference.

Inspection of Figure 1 gives an impression of biphasic action of l-isomethadone on the animal system. A special series of 23 rats given a dose of 3 mgm./kgm. showed no different results from a dose of 4 or 6 mgm./kgm. This biphasic action partly explains the different effects produced by l-isomethadone at the dose level of 2 mgm./kgm. Therefore, we cannot attribute the apparent strain differences to the animal systems, without further data, because

this biphasic action partly explains the different effects produced by l-isomethadone at 2 mgm./kgm. Smaller doses do not possess a marked effect on the intestinal tract; however, larger doses suddenly produce a large effect which shows no further change even with twice the dose producing that marked effect. Thus, 2 mgm./kgm. must be the threshold level of some powerful physiological or pharmacological mechanism which takes effect suddenly. At this dose level, the percentage of pylorospasms is changing rapidly, a factor which may or may not be related to this precipitous effect.

Table 1 also shows the inverse decrease in average distance traversed as the dose of this drug increases.

A "Straub-tail" effect was noticed at all dose levels and with most dose levels many rats showed exophthalmia. At a dose of 1 mgm./kgm. the intestinal tract appeared hyperemic in a number of animals. Considerable fluid was noticed in the intestines especially at the higher doses. Pupil size was variable especially at lower doses but as the dose increased, the pupils tended to be dilated. The cornea was dry at doses 3 mgm./kgm. or higher. Lacrimation was noticed at 3 mgm./kgm.; the corneal reflex was absent at the higher doses.

This drug caused convulsive deaths as follows: One at 2 mgm./kgm.; one (in 41 min.) at 4 mgm./kgm.; and two (55 and 60 min., resp.) at 6 mgm./kgm. Catatonia occurred for doses of 2 mgm./kgm or higher.

8. Alpha Acetylmethadol HCl. - At 2 mgm./kgm. dl-alpha acetylmethadol was responsible for an average carbon-black movement of 28.3%. There was a 10% incidence of "pylorospasm". In those showing

pylorospasm when the intestines were excised and the stomach manually squeezed, great force was required to force the stomach contents beyond the pyloric valve; however, this could also be demonstrated with other drugs in this series.

Pupil size was mostly unchanged at the lower doses. At 6 mgm./kgm. all pupils were dilated. Exophthalmia and xerophthalmia were noticed at 6 mgm./kgm.

At 4 mgm./kgm. this drug produced 70% "pylorospasm", this is of the same order of magnitude as similar doses of Heptazone(R) and l-isomethadone (Table 2, Figure 2). While it appears that one 1 mgm./kgm. (Figure 1) has more effect than 2 mgm./kgm., inspection of Table 1 will show that this is not a significant difference.

Catatonia was general for all doses above 2 mgm./kgm. with a strange "spread eagled" condition of the hind limbs noted in many animals at 2 mgm./kgm., when sacrificed, but not noticed at the higher doses because of the persistence of catatonia at the sacrifice time. However, at 4 mgm./kgm., the hind feet in many animals showed convulsive jerking after cutting the spinal cord in the thoracic region.

Hyperaemia of the mesenteries was general for the 6 mgm./kgm. group of animals, and the intestines contained large amounts of fluid. At 4 mgm./kgm., one death occurred before the experiment was finished and one animal was cyanotic and cold. While none died at 6 mgm./kgm., two had their teeth tightly clamped on the wire screen floor of the cage, and another was very cyanotic, and might presumably have died had not the experiment terminated at that point.

Apparently, Alpha acetylmethadol is very irritating to the animal on injection because the rats rubbed the injection site with their paws and appeared to be slightly irritated.

Under the experimental procedure used, a high incidence of intussusception was noticed with Alpha acetylmethadol.

9. Nalline-Merck (N-allyl-normorphine). - Examination of Figure 1, in which Nalline is plotted at one-tenth the dose administered, tends to show that by measurement of intestinal motility with the Macht method, Nalline has similar activity but 1/10 the power of the morphine molecule.

Figure 2, however, in which Nalline is plotted at 1/20 the administered dose, shows that for the condition of pylorospasm, Nalline has 1/40 the morphine effect in the Sprague-Dawley strain. However, the 100% point is statistically unreliable and further data is needed before this curve is accepted.

It is of interest that in the Wistar strain one pylorospasm was recorded in a group of 10 rats at a dose of 4 mgm./kgm. The marked difference which might be attributed to the different strains of rats used is apparent, and so far inexplainable, only for Nalline. At a dose level of 2 or 10 mgm./kgm. the Sprague-Dawley group response was between 50 and 60% while 4 or 10 mgm./kgm. in the Wistar group produced an average of 34%. Apparently, the drug is more potent for the Wistar animals.

The "Straub-tail-Effect" was noticed with all doses of Nalline but was general at doses above 10 mgm./kgm.

A high incidence of intussusception was noticed in this series as well as exopthalmia and a high incidence of fluid-filled intestines.

10. Heptazone. - This drug at 4 mgm./kgm. produced a cataleptic condition in the animals with a "Straub-tail" and a high incidence of dilated pupils. "Pylorospasms" were present to the extent of 60%. The average of the other four animals was 51.4%. This is a high average and may be due to a selective factor or the sudden precipitation of pylorospasms. The intestines of this group of animals were in general, relaxed and hyperaemic.

At 2 mgm./kgm. there were only 22% of the animals in whom the carbon did not pass the pylorus. The average was 47.7. Several animals of this series were cyanotic and the blood was noticeably discolored. At 1 mgm./kgm. the animals all had "Straub-tails" but in general they were otherwise normal appearing. Many had dilated pupils, but in general there was little pupillary effect. The average distance traversed by the meal was 62.1%.

D. The Antagonistic Effect of Nalline$^{(R)}$ on the Action of l-isomethadone and dl-Alpha acetylmethadol on Rat Intestinal Motility

1. l-isomethadone vs. Nalline.

When rats were given a dose of 4 mgm./kgm. of l-isomethadone and then one-half hour later either 2 or 4 mgm./kgm. of Nalline$^{(R)}$, the usual constipative effects of l-isomethadone were markedly counteracted. As previously mentioned (Table 1) when given alone, 4 mgm./kgm of l-isomethadone allowed the carbon meal to traverse only 8.9% of the intestinal tract in an hour with 66% of pylorospasms being produced.

Upon the administration of 2 or 4 mgm./kgm. Nalline, after this dose of l-isomethadone, the average traversed was 26% with only about

33% showing pylorospasm. Eight mgm./kgm. Nalline given at the same time as the carbon meal was slightly more effective, as shown in Table 3.

2. Alpha-acetylmethadol vs Nalline.

At a dose of 4 mgm./kgm. dl-alpha acetylmethadol reduced intestinal motility to the extent that, in those without pylorospasm, the intestinal contents progressed only 10.2% of the intestinal tract in an hour. At the same time this dose produced 68% pylorospasm.

Nalline in doses of 4 or 8 mgm./kgm. given at the time of the carbon meal and after dl-alpha acetylmethadol allowed the intestinal contents to progress beyond 40% while pylorospasms were reduced to 16%.

Higher doses of Nalline, 20 and 40 mgm./kgm., blocked out the pylorospasm response to alpha acetylmethadol but had but little more effect on the motility. These effects at higher dosages may be the result of the rapid destruction of Nalline in the body; two small doses may have effects similar to these larger doses. The point is better shown by the portion of Table 3 showing the results for Wistar strain rats. Here it is obvious that 4 mgm./kgm. alpha-acetylmethadol followed by 8 mgm./kgm. Nalline at the time of the carbon meal produces a result identical with that of the S-D Strain. In the group in which 8 mgm./kgm. Nalline was injected first, then a half hour later alpha-acetylmethadol 4 mgm./kgm. with the carbon meal being administered an hour after the Nalline, an average of 32.9% of intestinal tract distance with 16% pylorospasm was found.

When 4 mgm./kgm. each of Nalline and alpha acetylmethadol were mixed and given together there were no pylorospasms and the average for distance traversed was 42%.

E. Observations on Wistar Strain Rats.

1. Intestinal Motility.

Table 4 shows the results obtained using Macht's method when these drugs were used in the Wistar strain. A comparison is made for similar doses given the Sprague-Dawley strain. Two columns, one for the number of Wistar animals showing pylorospasm and one for the percentage expression of that number in relation to the total group permit tabulation of this data with that for motility.

a. Controls. - For 44 Wistar controls, the average distance traversed by the carbon meal in an hour is 61.2 $\pm$ 1.6 (S.E.). Comparing this with the average of 64 $\pm$ 0.7 (S.E.) for the Sprague-Dawley Strain, we find that the "T" value equals 1.75 which allows only about a 9% chance of the Wistar strain being different from the Sprague-Dawley.

b. Morphine Sulfate at 2 mgm./kgm. - There is no significant difference between 30.1% for the 32 Sprague-Dawley Rats and 28.9% for the 12 Wistar Rats.

c. L-isomethadone at 2 mgm./kgm. - The group of 23 Wistar rats exhibited inhibition of intestinal motility to the extent that the carbon meal progressed only 27.6% of the intestinal length in an hour. Considering the fact that one group of 10 Sprague-Dawley rats had an average of 32.0%, and that inspection of the

l-isomethadone dose-response-curve (Figure 1) could lead to the conclusion that 2 mgm./kgm. is a threshold dose for a powerful physiological mechanism, opinion as to strain differences must be reserved until further data is assembled.

d. Alpha acetylmethadol. - There is no significant difference between the average of 28.3% for the 34 Sprague-Dawley rats and 23.6% for the 22 Wistar rats at a dose level of 2 mgm./kgm. The same may be said for the dose of 4 mgm./kgm.

e. Nalline. - When the distance traversed by the carbon meal in an hour is compared in the two strains of rats, we find that the average distance of 57.1 ± 3.9 (S.E.) for 15 Sprague-Dawley Strain, when contrasted with the response in 19 rats of 34.0 ± 4.3 (S.E.) for the Wistar strain, produces a "T" value of 3.8. This has a probability level of greater than 0.005.

The same order of magnitude of response can be seen with the other doses of 2 and 4 mgm./kgm. Apparently, this dose-response difference is present at low doses. Further work is needed before this difference can be explained for the strains and for the drug.

It hardly seems possible that Nalline alone will give a strain-different response while the other analgesics do not.

2. Incidence of Pylorospasm in Wistar Rats.

a. Controls. - The 44 control rats showed no pylorospasm; this is similar to the observation on the Sprague-Dawley strain controls.

b. Morphine Sulfate. - None of its 12 rats given 2 mgm./kgm. of Morphine Sulfate showed any pylorospasm. This probably is not significant. Two groups of Sprague-Dawley rats, one with 7 animals, the other with 12, showed no pylorospasms. Apparently this is a threshold dose area.

c. L-isomethadone HCl. - Only one rat of the 24 given this drug at 2 mgm./kgm. showed this effect, or 4.2%. This is similar to the 4.7% shown for the Sprague-Dawley's.

d. Alpha acetylmethadol. - At 2 mgm./kgm, 6 (21.4%) of the 28 rats showed pylorospasm while at the dose of 4 mgm./kgm., 3 (30%) of the 10 rats showed this. It is to be noted that at 2 mgm./kgm. the incidence of pylorospasm is twice as high in the Wistar rats as the Sprague-Dawleys, but only half as high at 4 mgm./kgm. However, the data is insufficient to attempt a comparison.

e. Nalline. - At 4 mgm./kgm., one animal (10%) in a group of 10 had pylorospasm, but none of the 19 at a dose of 10 mgm./kgm. showed this response. No Sprague-Dawley animal showed pylorospasm below 120 mgm./kgm. At the present time there is insufficient data to attempt an explanation.

f. Summary. - In general, it may be said that with few exceptions (notably the Nalline response), there is little difference in the strain of rat used in testing the effects of these analgesic drug.

F. Conclusions:

The following conclusions may be drawn from the study of the effects of several analgesic drugs on the rat's intestine using Macht's Method in Sprague-Dawley and in Wistar strain rats:

1. The synthetic analgesic drugs, like morphine decrease motility in the intestinal tract. The intestinal motility is inversely proportional to the dose administered.

2. The synthetic analgesics tested (alpha acetyl-methadol and l-isomethadone) exhibit a biphasic action which has a threshold at about 2 mgm./kgm. Below this dose, the l-isomethadone is less constipating than morphine, above this dose range, more constipating.

It is conceivable that l-methadone, dl-methadone, and dl-isomethadone might exhibit this same activity, but such an assumption should be subjected to experimental inquiry.

3. Pylorospasm, a condition in which the charcoal meal does not pass the pylorus in the hour test period, was a property of all analgesics tested in this study. The incidence of this condition is directly proportional to the dose administered. Morphine apparently allows an intermittent interruption of this process at higher doses, probably due to local anoxia.

4. A close correlation or a good explanation was shown for the results obtained in the two strains of rats (Wistar and Sprague-Dawley) used in this study except for the effects of Nalline. We can offer no explanation for the persistent strain difference exhibited to this drug.

IV. A Study of the Effects of Various Analgesics on the Intestinal Motility in the Rabbit Using Eddy's Method.

A. Procedures and Modifications of Eddy's Method Used.

When this phase of this study was first undertaken using rabbits, the method used was that of Eddy modified by Sato's recommendation that the production of scybala by a group of rabbits in a given time be tabulated. This was attempted for several weeks during which time it was noticed that scybala counts made during the daytime were either very low with the majority of animals failing to defecate at times for periods of several hours or the faeces were passed in a soft malformed mass so that individual scybala could not be counted. It was thus practically impossible to obtain normal scybala counts for control values during the daytime. Consequently, on this basis and reasoning that the rabbit (Lepus) still retains its nocturnal habits, it was decided to carry out the observations from 5:00 PM. on, at night.

For each separate determination to study drug effects on the intestinal motility in rabbits, groups of 16 rabbits were used. The procedure followed was to perform the control observations, using saline injections, on a group of animals and, then, the following night to make scybala counts over a period of time following drug injection. In this way, each group of 16 rabbits served as its own control. For many of the earlier studies, the rabbits were given the saline or drug injection at 5:00 PM. Scybala counts were then made at the end of three and again four hours later for a total observation period of

seven hours after injection. Later in this study it was noticed that more detailed information might be obtained by making scybala counts consecutively at the end of one, three, five and seven hours after drug injection.

In the case with the use of one drug, alpha acetyl methadol, it was found necessary to extend the observation period to fifteen hours because of the marked constipative effect of this compound in rabbits, as evidenced by a noticeable decrease in the production of scybala during this time. In some instances, the scybala counts for the trial with alpha acetyl methadol could not be made until twenty hours after injection; practically, this difference in five hours is insignificant because of the normally low daytime scybala production.

Following each separate determination of the number of scybala passed by a group of rabbits per unit time, the results were tabulated and by accumulating this data the gross averages obtained. This method of evaluation is not as accurate as would have been possible had the results been expressed as a deviation from an average of the closest three control periods for the particular group under study. This latter procedure would have eliminated the small variation in group average scybala counts due to seasonal (longer or shorter days) drift of data which may have occurred since this study extended over more than one year's time. However, this gross compilation and averaging of the accumulated data, especially for the normal control values, was considered adequate for this study.

The presence or absence of food intake by the rabbit effects significant differences on the production of scybala. When the rabbits

are allowed food during a study period, it is difficult to distinguish whether it is the anorexia, with reduced food intake, or the constipative effect of the drug which causes a reduction in the scybala count. Of course, more marked changes in intestinal activity would be expected after drug administration than caused by starvation alone. In view of the fact that a majority of patients on morphine therapy will have to eat and, if this information is to apply to ultimate therapeutic use, it would, therefore, seem more appropriate and informative to carry on such a laboratory study with food offered ad lib. In spite of the objections and difficulties encountered when food is allowed the rabbits during an experimental period, this procedure was followed.

In the discussion that follows the presentation of the results in some of the graphs and tables shown below, reference is made to certain of the drugs producing a "high tonus" or a "low tonus" type of constipation. High tonus constipation might be considered to be the same effect which has been recorded by balloons and water transport studies. Above certain threshold doses the opiate analgesics will characteristically show an increased tonus and occlusion of the lumen. This increased tonus causes a hard bolus or formed faecal mass to be propelled more rapidly. This is represented by an immediate increase in scybala production in many rabbits, herein assumed to be those having formed pellets in the colon. Since the semifluid contents are obstructed by the closed lumen, no scybala are then passed for several hours.

By low tonus effect, we would mean that dose range which Krueger reported to caused a decrease in the tonus as recorded by balloon

experiments. In this case, the hard bolus would not be propelled by the relaxed musculature, and the pellet production would be normal, or less than normal because of the lack of motility. In this case, many formed scybala would be passed in the second collection period as noticed at the lower dosage levels.

B. Experimental Results Using Eddy's Modified Method of Making Periodic Rabbit Scybala Counts As An Index of Intestinal Motility.

1. Description of Results Presented in Graphs and Tables.

The results of this phase of the study are presented by means of a number of tables and graphs, as follows:

a. Table 7. - This table is a compilation of all data obtained during that part of this study employing observations of scybala counts in the rabbit to study intestinal motility. It shows the accumulated gross averages for the saline injected control animals and the effect of different dose levels of alpha acetylmethadol, l-isomethadone, morphine sulfate and N-allyl-normorphine on the average results of the tabulated scybala count for definite periods of time in the rabbit. Time intervals of observation are 3, 7 and, where determined, 15 hours after injection. Where a recorded effect is not the property of all observations of the larger group, the number of observations for which the record applies have been separately listed. These separate groupings may or may not overlap.

Control studies in the saline injected animals showed that

TABLE 7

THE EFFECT OF CERTAIN ANALGESIC DRUGS ON THE AVERAGE NUMBER OF SCYBALA EVACUATED OVER PERIODS OF TIME IN RABBITS.

DRUG	DOSE	NO. OF OBSERVATIONS	AVERAGE NUMBER OF SCYBALA FOR PERIODS AFTER DRUG INJECTION 0-3 hrs.	3-7 hrs.	0-7 hrs.	7-15 hrs.
	mgm./kgm.					
Saline Control	0.2 cc/kgm.	664	60.8	87.3	148.1	-
" "	" "	126	-	-	-	119.0
" " **	" "	48	28.4	21.7	50.1	-
Alpha Acetyl-methadol HCl	0.5	16	5.8	18.6	24.4	124.0
"	1	15	17.8	7.1	24.9	71.6
"	2	32	11.3	5.8	17.1	50.1*
l-isomethadone HCl	0.5	16	16.5	91.6	108.1	-
"	1	16	26.7	91.1	117.8	105.3
"	2	30	23.8	26.0	49.9	-
Morphine Sulfate	0.05	16	45.7	87.6	133.3	-
" "	0.5	16	18.1	103.9	122.0	-
" "	1	32	18.3	77.7	96.0	-
" "	2	59	17.0	27.0	44.2	-
" "	2	30	-	-	-	146.4
" " **	2	16	6.6	13.3	19.9	31.3
" "	6	23	13.2	17.8	31.0	121.3
N-Allyl-normorphine HCl	2	16	17.4	97.6	115.0	-
"	4	15	12.5	68.9	81.4	109.0
"	20	16	5.7	33.9	39.6	121.3

* observation at 20 hours.
** food removed at time of injection of drug.

when the rabbit is fed ad lib, the approximate average number of scybala passed per hour is twenty (estimated by dividing the number of hours in each observation period into the average number of scybala for that period). The deviation from this average figure of 20 scybala per hour produced by administration of a drug may then be considered in comparison with this norm.

b. Table 8. - While the data presented in this table has also been included in the previous table 7, the results shown here are for shorter individual periods of observation with the scybala counts being made at 1, 3, 5, 7, and 15 hours after drug injection. A comparison with table 7 will immediately show that abundance of comparative information which the shorter periods of observation provide. This is especially evident for the scybala count made for the first hour since it permits a differentiation between the high tonus and the low tonus type of constipation considered earlier.

By comparing the number of scybala passed in the first hour with the number shown for the next two hours in table 8, it is seen that l-isomethadone and alpha acetylmethadol have a high scybala count in the first period followed by a lower count in the next period at higher doses. Lower doses, however, tend to reverse this effect. While not so apparent with morphine the same trend may be discerned. The gradual slope of the morphine dose-effect curve for the rat studies shown in figure 1 as contrasted with the steep slope for

l-isomethadone and alpha-acetylmethadol may be seen to have a counterpart in these rabbit graphs, though not expressed in the same manner. This qualitative difference of response, affecting as it probably does many physiological mechanisms could easily account for the slight differences seen here.

In order to more clearly picture this material, several graphs have been constructed for selected groupings of the data shown in table 8:

1. Figure 4. - The several graphs in this figure show the effect of comparable doses of the various analgesic drugs used on the rabbit's intestinal motility as measured by the average number of scybala passed per hour in each collection period. With this graphic method of comparison it is seen that l-isomethadone at 2 mgm./kgm. is less constipating than morphine, and alpha acetylmethadol more constipating when given in the same dosage. N-allyl-normorphine, administered in a dosage at ten times that shown by its position on the graph (i.e., 2 mgm./kgm. X 10 = 20 mgm./kgm. actually administered), corresponds roughly with the effect of morphine at 2 mgm./kgm. which follows the one to ten ratio found in the rat studies. However, it may be noticed that the production of scybala during the first hour is markedly inhibited instead of potentiated. We therefore class this as a low tonus constipation.

2. Figure 5. - This graph portrays the effect of the various

doses of morphine used on the rabbit's intestinal motility. The graphs show the relationship of morphine dose to intestinal effect and, further, depicts the sensitivity of this method of measuring the response to graded doses of an analgesic in the rabbit. At the low dose of 0.05 mgm./kgm. morphine was found to be somewhat stimulatory (high tonus effect) during the first hour observation period but this slight effect is lost when comparison is made to the gross control average instead of the average of the nearest three controls. This first hour reading is the one affected by the variations in daylight hours. The downward displacement of this 0.05 mgm./kgm. curve is an effect of the drug and is not to be found in control records. We therefore must class this dose as still constipating.

3. Figure 6. - This graph shows the effect of different doses of l-isomethadone and alpha acetylmethadol on the intestinal motility of the rabbit, expressed as average scybala count per hour. All doses of alpha acetylmethadol used were more constipating than l-isomethadone. It should be noted, however, that the doses used here are comparatively greater than the clinical dose used in the human and, therefore, might well be above the threshold of intestinal effect reached with clinical doses. A marked continuation of the drug inhibitory effect is apparent with alpha acetyl methadol.

4. Figure 7. - This graph shows the effect of Nallive(R) in increasing doses on the intestinal motility of the rabbit. This re-

sult suggests that clinical use of Nallive(R) might show intestinal sequela. It might be noted that all doses tested show a low production of scybala during the first hour which is in contrast to the other analgesics.

TABLE 8

THE EFFECT OF CERTAIN ANALGESIC DRUGS ON THE NUMBER OF SCYBALA EVACUATED BY RABBITS OVER SHORT PERIODS OF TIME DURING A FIFTEEN HOUR OBSERVATION PERIOD.

DRUG	DOSE	NO. OF OBSER-VATIONS	AVERAGE NUMBER OF SCYBALA FOR PERIODS OF TIME (hours) SHOWN AFTER INJECTION 0-1	1-3	3-5	5-7	Totals 0-7	7-15
Saline Control	-	287	18.0	39.1	49.5	43.3	149.9	-
0.2 cc./kgm.		126	-	-	-	-	-	119.0
Saline *	-	48	9.5	18.9	12.4	9.3	50.1	-
" *	-	16	Food replaced at midnight				-	204.8
" *	-	16	-	-	-	-	-	19.5
" *	-	16	9.8	20.0	12.9**	45.5	-	-
Alpha Acetyl-methadol HCl	0.5	16	0.5	5.3	6.7	11.9	24.4	124.0
"	1	15	17.6	0.1	1.8	5.3	24.9	71.6
"	2	32	11.0	0.2	0.8	5.0	17.1	50.1***
l-isomethadone HCl	0.5	16	7.5	9.0	52.1	39.5	108.1	-
"	1	16	18.6	8.0	32.7	58.4	117.8	105.3
"	2	16	22.0	10.4	8.6	18.8	60.0	-
Morphine Sulfate	0.05	16	14.8	30.9	37.7	49.9	133.3	-
" "	0.5	16	9.0	9.1	51.1	52.8	122.0	-
" "	1	32	11.0	7.3	29.9	47.8	96.0	-
" "	2	32	7.7	4.6	6.3	15.3	34.1	-
" "	2	30	-	-	-	-	-	146.4
" " *	2	16	6.5	0.1	4.5	8.8	19.9	31.3
" "	6	16	5.2	0.1	1.3	18.5	24.7	125.9
N-Allyl-nor-morphine HCl	2	16	3.4	13.0	38.6	59.0	115.0	-
"	4	15	5.3	7.2	32.8	36.1	81.4	109.0
"	20	16	0.4	5.3	6.6	27.3	39.6	121.3

* Food removed at time of drug injection.
** Food replaced at the 5th hour.
*** Observations made at 20th hour.

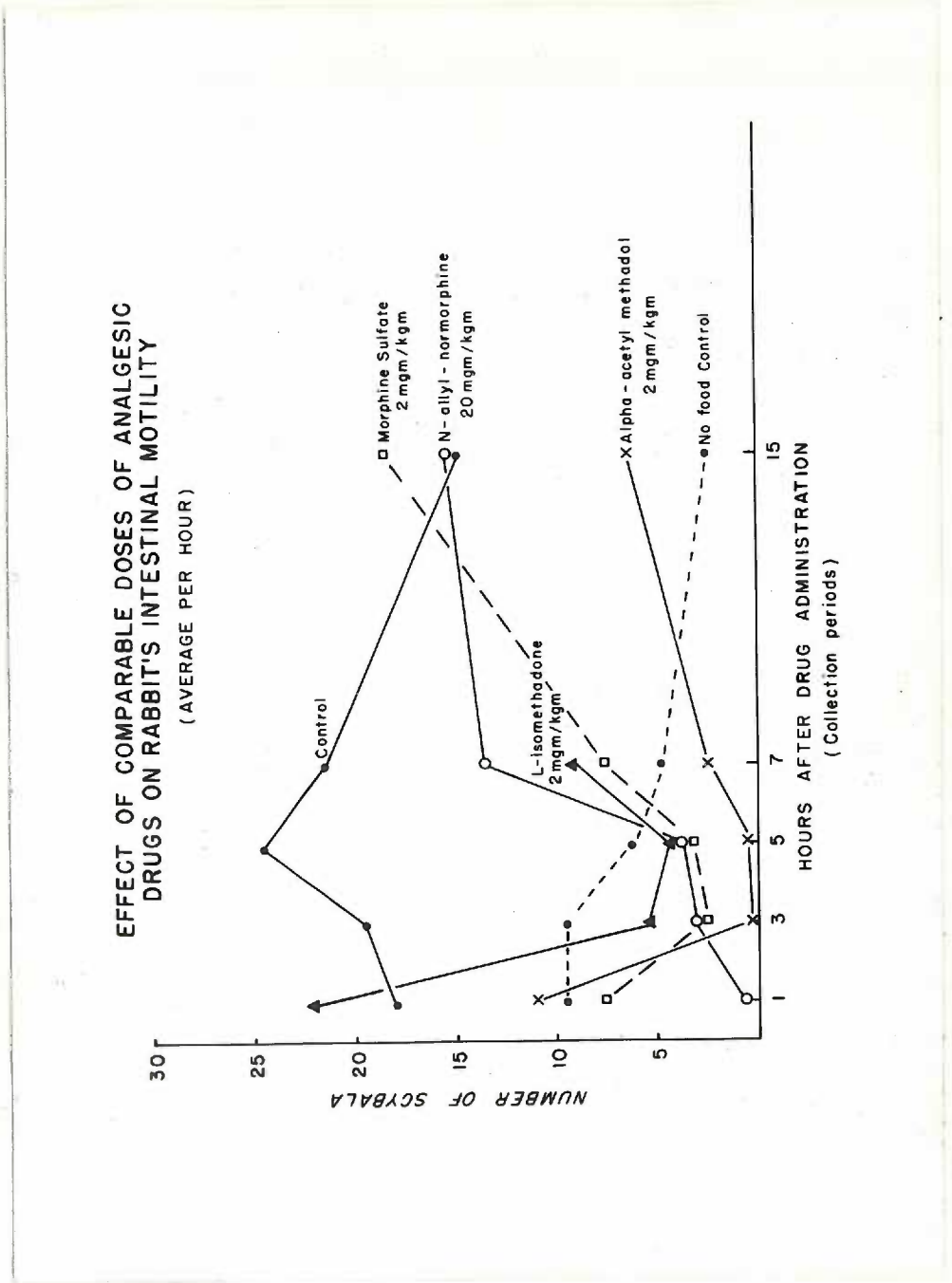


Figure 4. The effect of comparable doses of analgesic drugs on the rabbits intestinal motility.

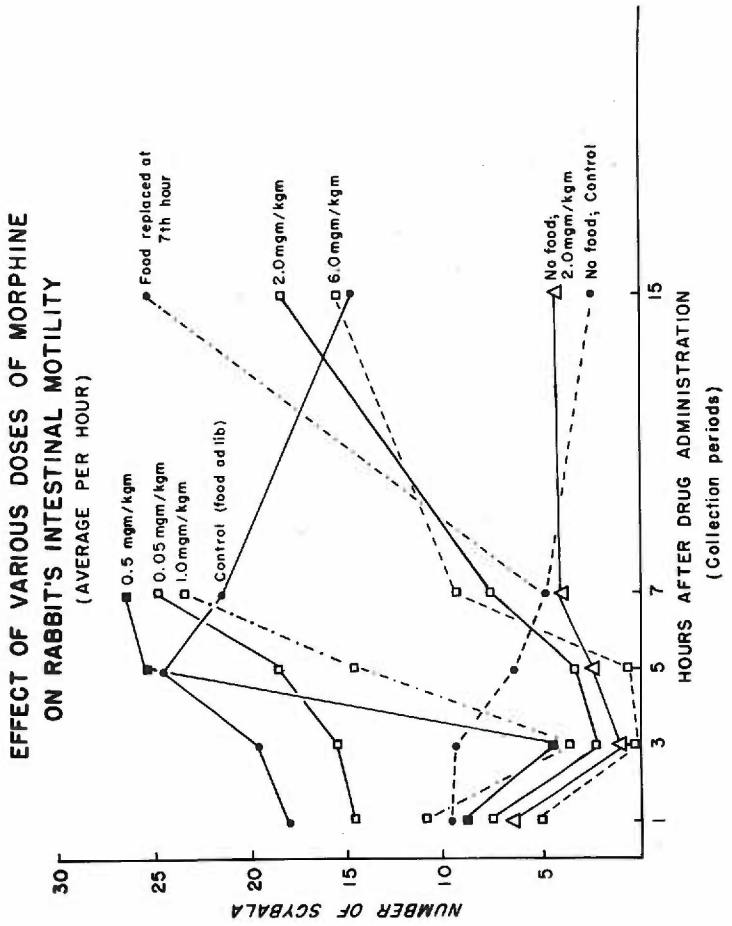


Figure 5. The effect of various doses of morphine on the rabbit's intestinal motility.

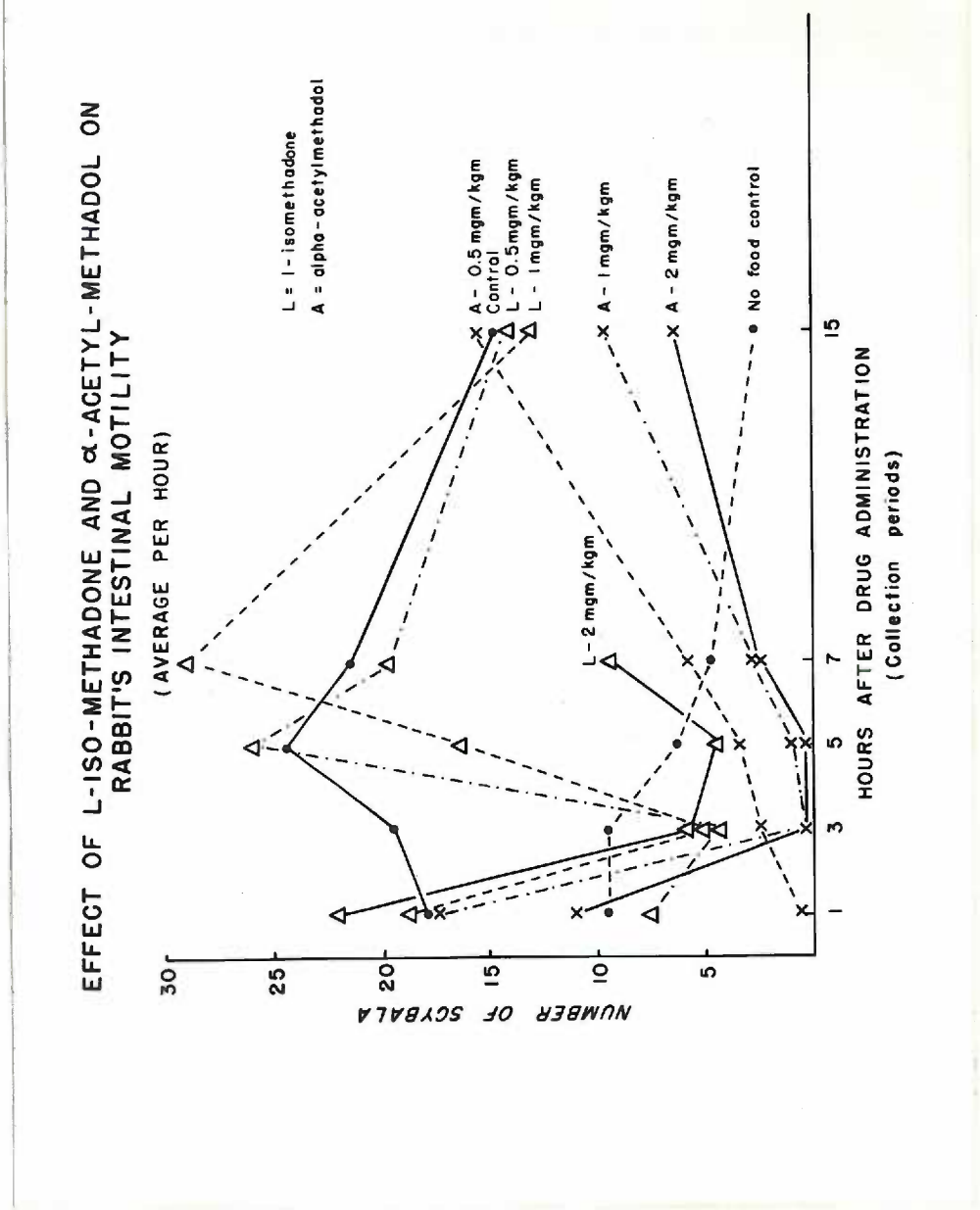


Figure 6. The effect of l-isomethadone and alpha-acetyl methadol on the intestinal motility of the rabbit at various doses.

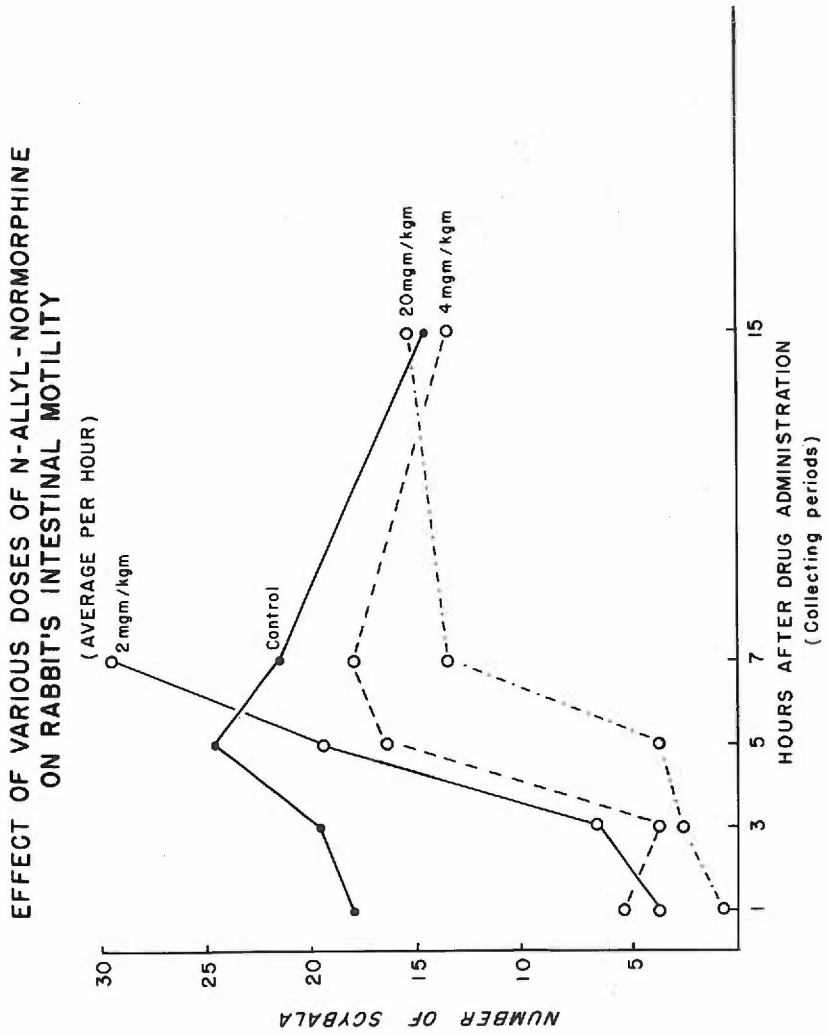


Figure 7. The effect of various doses of N-allyl-normorphine on the intestinal motility of rabbits.

c. Table 9. - It is not unusual to find a few rabbits which produce no scybala during the observation period, but usually the number of animals in this catagory is small. These noncontributors are calculated as a percentage of the total number of rabbits tabulated. Therefore, a marked increase of nonevacuating animals following drug administration may, then, be considered as an index of the constipating effect of the drug.

1. Figure 8. - This figure shows the marked effect of comparable doses of the several analgesic drugs used in this study on the percentage of rabbits which failed to defecate during an observation period. The comparable analgesic dose of morphine 6 mgm./kgm.; l-isomethadone 2 mgm./kgm.; alpha acetyl methadol 2 mgm./kgm.; a weight comparable dose (2 mgm./kgm.) for morphine; and a ten-fold dose (20 mgm./kgm.) of Nalline(R) are plotted for comparative effects.

Two controls, one with food ad lib, and one without food during the observation period, are provided for comparison with the drug effects. By graphing the results in this way, it is seen that alpha acetyl methadol is the most constipating analgesic and l-isomethadone, the least. The no-food control tends to show that the anorexia produced by the drug is of little consideration in this study.

d. Table 10. - This table is essentially the same as Table 8 except that the averages do not include the non-defecating rabbits which are tabulated in Table 9. The purpose of this tabulation is to show that upon the administration of the analgesic, the

rabbit, with most dose levels and most analgesics will either suddenly produce great numbers of scybala in the first hour, or few or none at all. Exceptions to this effect are Nalline(R) and the low doses of the other drugs which, because of the decrease of intestinal tone they effect, fail to move the hard bolus faster than normal.

e. Table 11. - Frequently the mass averaging of data obscures trends which might otherwise be evident were additional data presented. This table shows the stimulating effect of the drugs used at high doses which produce immediate defecation. The trend at low doses of the drugs is to inhibit immediate defecation. Of course this tabulation has a definite disadvantage because the second period is a two hour period, while the first period is only one hour.

The control animals normally show a ratio of 1 to 5 or about 1 to 3 for the no food controls. Considering the statistical limitations of the small numbers presented, it is apparent that this ratio may still be seen for the lower doses but shifts markedly for the higher doses of the drugs tested. Nalline does not show this ratio shift.

TABLE 9

THE EFFECT OF CERTAIN ANALGESIC DRUGS ON THE PERCENTAGE OF ANIMALS PRODUCING NO SCYBALA DURING THE OBSERVATION PERIOD.

DRUG	DOSE mgm./kgm.	NO. OF OBSER-VATIONS	OBSERVATIONS IN WHICH NO SCYBALA WERE PASSED DURING OBSERVATION PERIOD EXPRESSED AS PERCENTS (%). 0-1	1-3	3-5	5-7
Saline	-	287	21	3	1	1
" *	-	48	39	10	12	22
Alpha Acetyl-methadol HCl	0.5	16	93	62	75	0
"	1	15	33	86	53	26
"	2	32	46	87	90	62
l-isomethadone HCl	0.5	16	50	6	6	0
"	1	16	25	37	6	0
"	2	16	37	37	25	0
Morphine Sulfate	0.05	16	12.5	0	0	0
" "	0.5	16	50	6	0	0
" "	1	32	37	18	3	3
" "	2	32	56	50	34	3
" " *	2	16	43	87	37	12
" "	6	16	81	94	56	12
N-Allyl-nor-morphine HCl	2	16	75	25	6	0
"	4	15	46	46	6	0
"	20	16	69	69	31	12

* Food removed at time of drug injection.

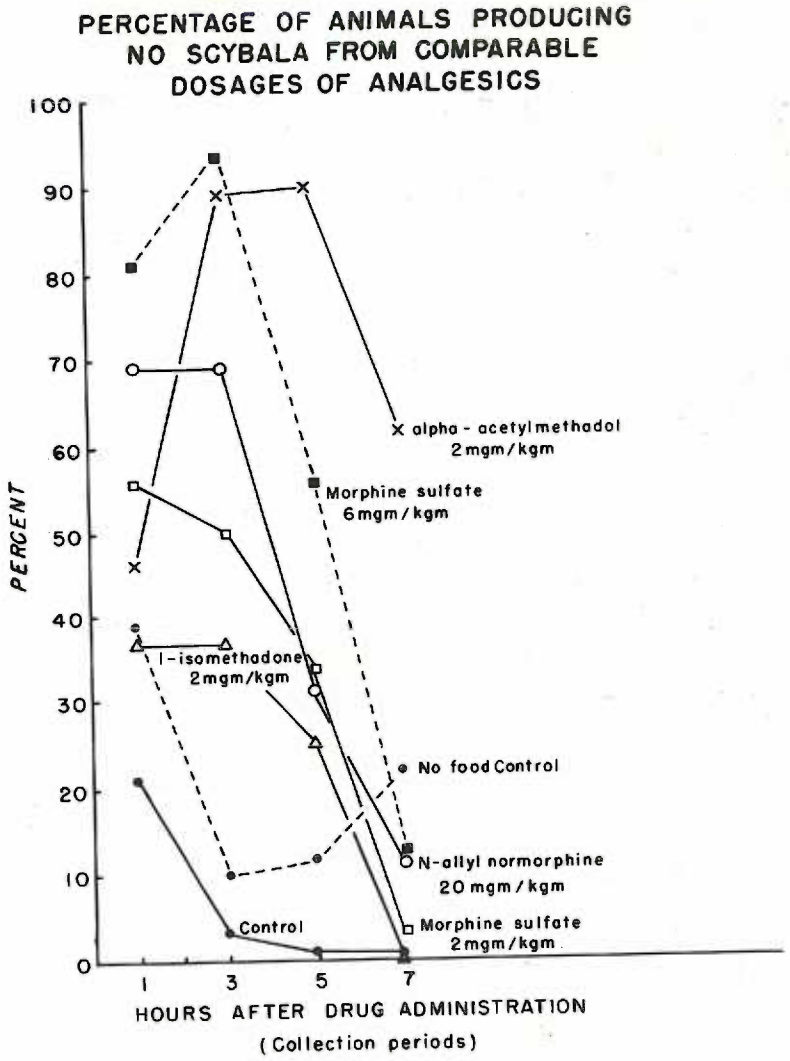


Figure 8. The percentage of rabbits producing no scybala after administration of comparable doses of analgesics.

TABLE 10

EFFECT OF ANALGESIC DRUGS ON NUMBER OF SCYBALA EVACUATED OVER SHORT PERIODS OF TIME DURING A SEVEN HOUR OBSERVATION PERIOD WHEN DATA ON RABBITS PRODUCING NO SCYBALA ARE REMOVED FROM THE CALCULATIONS.

DRUG	DOSE mgm./kgm.	NO. OF OBSER-VATIONS	AVERAGE NUMBER OF SCYBALA FOR PERIODS OF TIME AFTER INJECTION (hours) 0-1	1-3	3-5	5-7
Saline	-	287	22.8	40.7	50.0	43.0
" *	-	48	15.7	21.1	14.2	12.1
Alpha Acetyl-methadol	0.5	16	8.0	14.3	27.0	11.9
"	1	15	26.5	1.0	4.0	7.2
"	2	32	20.8	1.7	8.6	1.3
l-isomethadone	0.5	16	15.0	9.6	55.6	39.5
"	1	16	25.0	12.9	35.0	58.4
"	2	16	35.2	16.7	11.5	18.8
Morphine Sulfate	0.05	16	17.0	30.9	37.7	49.9
" "	0.5	16	18.0	9.7	51.1	52.8
" "	1	32	17.7	9.0	30.9	49.4
" "	2	32	17.7	9.2	9.6	15.8
" " *	2	16	11.6	1.0	7.2	10.1
" "	6	16	28.0	2.0	3.0	20.5
N-allyl-nor-morphine	2	16	13.7	17.4	41.2	59.0
"	4	15	10.1	13.5	34.1	36.1
"	20	16	1.4	17.0	9.6	31.2

* Food removed at time of injection.

TABLE 11

NUMBER OF RABBITS WHICH HAVE MORE SCYBALA IN ONE OF THE FIRST TWO COLLECTION PERIODS THAN THE OTHER OF THE FIRST TWO PERIODS.

DRUG	DOSE	NO. OF OBSERVATIONS	NUMBER OF RABBITS PRODUCING: a. more scybala in one period than the other		b. 10 or more scybala in one period than the other	
			0-1 hr.	1-3 hrs.	0-1 hr.	0-3 hrs.
Saline	-	144	22	117	16	90
" *	-	64	15	42	10	29
Alpha Acetyl methadol	0.5	16	1	6	0	3
"	1	15	9	0	6	0
"	2	32	17	3	10	0
l-isomethadone	0.5	16	3	13	2	5
"	1	16	9	3	7	3
"	2	16	10	4	8	4
Morphine Sulfate	0.05	16	3	13	2	7
" "	0.5	16	4	10	3	3
" "	1	32	16	11	10	4
" "	2	32	15	3	12	1
" " *	2	16	8	0	4	0
" "	6	16	3	1	2	0
N-allyl-normorphine	2	16	2	11	1	6
"	4	15	5	7	2	4
2	20	16	4	5	0	3

* Food removed at time of drug injection.

2. A Summary of Effects of Morphine, L-Isomethadone, Alpha Acetylmethadol and N-Allyl-normorphine on Intestinal Motility In The Rat.

a. Results on Control Rabbits. - The normal rabbit will produce about 20 pellets an hour over the long term average. The lower apparent hourly average for the 8 hour morning period would be higher could they be observed at an earlier hour because the production practically ceases with the advent of daylight. Two types of controls have been tabulated in the tables: One for animals fed ad lib and one in which the food was removed at the time of the drug injection. Fasting produces a marked effect on the average scybala production, but the effect is different from that produced by the drugs in that the average shows a steady decrease with time. The drugs show a marked initial depression with later recovery.

In Figure 8 it can be seen that fasting has little effect on the percentage of non-defecating animals while the drugs produce a marked effect. When food is withheld and then replaced at midnight, the animal almost doubles the 8 hour average scybala level and the total for the night is about the same as it would have been had he had access to food for the entire night. Even morphine 2 mgm./kgm. with no food shows this tendency when compared with the no food control. This effect is also seen to some extent with the drugs whose average is generally higher than the control average. As can be seen (Table 8), replacing the food at the 5th hour (10:00 PM.) returns the 7th hour average to normal.

b. Morphine Sulfate. - The effect of this reference drug has been determined at several dose levels in order to get a pattern of dose relationship to effect and to determine the sensitivity of the testing method. This is shown in Figure 5. The relationship of increased effect to increased dose is immediately apparent. Morphine is more constipating, when tested by this method, than l-isomethadone but less so than alpha acetylmethadol. Apparently morphine exerts a different effect during the day than at night, because contrary to the findings of Scott, et al (1947) (59), morphine sulfate at 2 mgm./kgm. was very constipating when tested by our modification. Even a dose of 0.05 mgm./kgm. was still constipating.

c. Alpha acetylmethadol. - By the rabbit scybala method of determining intestinal motility, this drug is more constipating at 1 mgm./kgm. than morphine at 6 mgm./kgm. Another effect of this drug noticed was that the majority of rabbits would sneeze and many had profuse nasal discharges following administration of this drug. This effect was not noticed in the other drugs tested. The animals also became stiff and catatonic, indicating a low grade opisthotony. Only one animal at 6 mgm./kgm. morphine sulfate showed opisthotony.

d. L-isomethadone. - This drug had the least effect on the intestinal motility of the three analgesic drugs tested in this series.

e. N-allyl-normorphine. - The effect of this drug at 20 mgm./kgm. roughly compares with the effect of morphine at 2 mgm./kgm. (Figures 7 and 8) both for reduction of the average number of scybala from normal and for percentage increase in the number of non-defecating

animals. This tends to strengthen the observation made with the rat motility procedure that N-allyl-normorphine has one-tenth the effect of morphine on the intestinal tract.

Another important factor is that Nalline(R) does not cause immediate defecation of the formed scybala which are in a position to be eliminated. Krueger (19) has pointed out that morphine derivatives at their lowest effective dose level will cause a decrease of intestinal tone and motility. Dog experiments in this laboratory have shown that Nalline(R) is no exception to this observation and that this effect is still present at doses greater than the 20 mgm./kgm. dose used for these rabbits. This decrease of tone instead of immediate stimulation of the lower intestine is shown by the lack of immediate scybala production for the first hour after drug injection. This can also be noticed for the low dose of A-acetylmethadol and l-isomethadone at 0.5 mgm./kgm.

3. Conclusions: - A modification of Eddy's technique, as outlined in this report, increases the sensitivity of the method for testing intestinal effects of morphine from the use of the high dose of 6 mgm./kgm. to 0.05 mgm./kgm. Drug intestinal effect may be compared with a high degree of efficiency by this method.

L-isomethadone is less constipating by this method of testing than is morphine at comparable doses. Alpha acetylmethadol at 1 mgm./kgm. is more constipating than 6 mgm./kgm. of morphine.

While the lower limits of sensitivity of this method have not been investigated, it is believed that this modified method will prove to be a sensitive and useful indicator of drug action on the intact intestinal tract.

DISCUSSION

I. A Consideration of the Constipative Effects of Analgesics Used in this Research.

The present or future clinical use of the newer synthetic analgesic compounds will depend considerably upon the incidence of side effects produced by the drug as well as by the efficiency of the drug itself as an analgesic.

This research was undertaken primarily to compare the side effects of the newer analgesics to the side effects of Morphine, with special emphasis on constipation. That has been done with a limited number of methods of comparison. At the same time differences of action must be noted. The morphine derivatives possess the same activity but in different degrees of effectiveness. The study which will separate the analgesic effects from the side effects is one which finds a difference in action and uses this separation of properties as an entering wedge to the solution of the problem.

A. Alpha Acetylmethadol. This analgesic is more effective in the l-form according to Fraser and Isbell (1950) (59) because the d-form appears to have a lag period before becoming effective. This lag effect was also observed by Sung and Way (1953) (60) in parenteral but not oral administration. Beecher and Keats (1952) (61) however, report the lag to be with the l-form and the description of the effect of their dose of 0.5 mgm./kgm. on human subjects wherein they became comatose was markedly greater than the effect on rabbits at that dose. However, their work also tends to point out the rapid increase

of systemic effect with increased dosages.

David and Semler (1952) (62) reported alpha acetylmethadol to be very effective clinically as an analgesic while constipation was not noticeable to a degree that could be evaluated. However, from the evidence which is presented in this thesis, it might be expected that alpha acetylmethadol would be very constipating although the doses were larger than the comparative amounts used clinically. The constipative effect is seen to decrease rapidly as the dose is decreased. Possibly the dose range (0.07 to 0.5 mgm./kgm.) employed for clinical use (and applying rabbit data to humans) is below the dose level where constipation is a factor.

B. L-Isomethadone. This recently developed analgesic has been used extensively by the army in Korea (Beecher et al, 1951) (63)) where it was found to be an analgesic about as effective as morphine but with fewer side effects. Keats and Beecher (1951) (64) found it to be similar to morphine for the depression of respiration. Denton, et al, (1948) (65) reported the side effects of 10 mgm. l-isomethadone given subcutaneously to have a higher correlation with the placebo than with a similar dose of morphine, "which indicated low toxicity."

The results of the studies in this thesis on the rabbit and rat tend to show that l-isomethadone has less constiapting effect than either morphine or alpha acetylmethadol, though the difference in the rabbit is not so evident as in the rat.

Since the only deaths in this series of tests have occurred in the isomethadone series, it might be a consideration in high doses for clinical use to watch for toxic manifestations.

C. Morphine Sulfate. This long-used analgesic has been used in this study as the reference drug for comparison and to serve as a control for observations made in the newer sythetic analgesics.

D. N-Allyl-normorphine Hydrochloride. Recently given the proprietary appellation of Nalline(R), this compound was first synthesized in 1940 by Dr. Elton L. McCawley, Associate Professor of Pharmacology, University of Oregon Medical School (66). Hart and McCawley (56) were the first to investigate the pharmacologic properties of Nalline(R). They found that it, like N-allyl norcodeine (first prepared by von Braun in 1914), antagonized the effects of morphine. Weijlard and Erickson (67) also reported the synthesis of n-allyl normorphine in 1942.

Other reports of studies of the antagonistic effect of Nalline(R) to the opiates have been extended to include all opiates and synthetic narcotics so far tested (68-81) with a review by Vernier (82).

II. A Consideration of Constipation.

Intestinal motility has been reported to be decreased by emotional states, anxiety, rage or distress (respiratory tract occlusion) (13,12); distention (83); anoxic anoxia (41), deficiency of Sodium Chloride (28); decrease of blood volume by 20 o/o or decrease of plasma proteins (84); vagotomy (85); CO_2 (36); CO (34); by Pentothal and es-

pecially ether anaesthesia (27); Ephedrine (42); amphetamine (25, 45,86); epinephrine; atropine (42,87); Tetraethylammonium chloride (38); and even after placebos (20,89,90,91,92). Ergotamine and prostigmine (42) increase motility while the increase observed with Sodium Amytal(R) is probably due to the effect of this drug which has been reported to speed the emptying time of the human stomach (93), but there is also the possibility of a central release of anxiety. Thus, it can be readily seen that intestinal motility is decreased markedly by conditions which discharge the sympathetic system of the organism as well as a great number of sympathomimetic drugs, or by conditions which block the normal cholenergic effects.

Contrary to most prevalent ideas, the absence of vagal effect often produces pylorospasm, as shown by Deaton and Bradshaw (85), and the spasms are not reversed by atropine, Banthine(R) Procaine, Trasentin or Pavatrine, but anaesthesia will relax the sphincter. Sato (51) similarly showed that vagal section in rabbits did not prevent morphine constipation, but that removal of the coeliac ganglion or section of the spinal cord between C-7 and T-1 would abolish the constipating effects of morphine.

This is in line with the observation that morphine discharges the sympathetic system producing a rise in blood sugar which reaches a peak in one hour and with the hyperglycemic response lasting for several hours. Hypertrophy of the adrenals is produced by prolonged administration of narcotic analgesics. Further evidence along this

line is that removal of the adrenals markedly decreases the analgesic response to morphine. Nitta (1952) (94) has throughly reviewed the studies on the hyperglycermic response to narcotics.

This hormonal component of analgesia has been explored by Winter and Flataker (95) who found that desoxycorticosterone acetate enhanced the effect of analgesia while cortisone the adrenocorticotropic hormone decreased the analgesic effect of the opiates.

The labyrinth has a profound effect on the duodenum as has been shown by Ingelfinger and Moss (1942) (23), because caloric or galvanic stimulation will cause immediate contraction of the duodenum, as does morphine when it is administered.

Morphine, meperidine and methadone produced a marked increase in the sensitivity to these labyrinthine tests (96) and made the mechanism so sensitive that even ambulation following the administration of these drugs increased markedly the incidence of nausea and vomiting in patients (97). This central effect could be blocked by Dramamine(R), however, in the case of nausea and vomiting. While this effect of the labyrinth stimulation on the duodenum which can be augmented by morphine needs proper evaluation, it is an effect of a transitory increased tone and will not be further evaluated in this discussion.

The observations of Abbott and Pendergrass (20), and of Gruber et al, (58) showed that clinical doses of morphine caused an immediate duodenal spasm which lasted up to thirty minutes followed by a prolonged period of dilatation which lasted for 4 or 5 hours (even detectable

for 24 hours). This period of decreased tone was presumed by Abbott and Pendergrass to be the chief cause of constipation. Krueger reported that the first response to a minimal dose of morphine or its derivatives is that of decreased tone and motility. In the dog the morphine dose that produces this effect is in the range of 0.01 to 0.04 mgm./kgm.

In Sumwalt's (5) review of the fate of morphine, it is pointed out that the kidney immediately starts to dispose of the drug, but at a decreasing rate as the blood level decreases. Therefore, while 70 o/o of the administered morphine is excreted in the first day, morphine is still detectable in the urine for 4 days. Epinephrine immediately reverses the spasm and motility due to morphine, even at high morphine doses. This effect, like the epinephrine effect on the blood pressure, is transitory, lasting only as long as the concentration of the drug remains high. This effect has also been mentioned previously by Plant and Miller (16) and Vaughan Williams and Streeten (98).

We now have a picture of a clinical dose of morphine (0.2 mgm./kgm.) producing immediately an increased tone or spasm in the duodenum which lasts up to 30 minutes; a discharge of epinephrine from the adrenals which produces a hyperglycermia which reaches a peak in an hour.

While it is doubtful that the body can produce enough epinephrine to reverse the intestinal spasm effect of morphine in high doses, it is apparent that the decreasing morphine concentration in the body

coincides with an increasing epinephrine level, as judged by the blood sugar rise, at which time the intestinal tract develops a state of prolonged atonia which, along with the hyperglycemia, lasts for many hours.

Either the morphine blood levels produced by the dose of 0.2 mgm./kgm. are decreased by kidney excretion and other metabolic processes to the order of blood levels produced by 0.01 to 0.04 mgm./kgm. with the resultant decreased intestinal tone or the epinephrine reaches a ratio of effectiveness at which time the intestinal tract will have a decreased tone and motility. Further evidence of the involvement of the sympathetic system is that the pressor sympathetic response blocking agents tend to potentiate the analgesic effects of these drugs. This has been shown by David and Semler (1952) (99). The evidence presented by Smith and Penrod (35) that Amphetamine at low doses reduces the activity of isolated intestinal strips, while high doses increase activity may well point out the need of future studies on the effect of epinephrine in the problem of intestinal tonicity.

The morphine induced intestinal spasms which are obtained from isolated strip experiments are not reversed by epinephrine or by atropine, but these morphine concentrations are beyond those possible in vivo, and represent toxic symptoms. Vaughan-Williams has shown that atropine in vivo is not effective against morphine above concentrations of 0.32 mgm./kgm., but that it will reverse the effect

below that level. This is in the range of the spastic or increased tone effects of the drug, which may well be cholinergic. Above that level, the direct action of morphine on the smooth muscle may play a part and prevent atropine reversal. The anticholinesterase effect of morphine may not be too important in the constipation effect because Nalline(R), as reported by Blohm and Willmore, (1951) (100) has a slightly greater anticholinesterase effect than morphine.

Considering the fact that opium was used for centuries as a specific for diarrhoea and dysentery, and paregoric is still used for this effect, at dose levels below that required for analgesia, we find that an important factor in constipation is the lack of tone and motility produced by low doses of the opiates. The intestinal spasms seen at higher doses in the laboratory animal, and the transitory spasm seen with clinical doses of morphine may be a secondary consideration in opiate constipation.

The point of attack for relieving this effect of constipation, therefore, is not to try to relieve the spasm which is transitory but to prevent the lack of tone and motility which lasts for hours and against which cathartics are ineffective and may be dangerous, (17).

Of course the reduced secretion and increased threshold to the defecatory stimulus contribute to constipation, but lack of motility is perhaps the largest factor.

III. Consideration of Antagonistic Effects of Nalline(R) on Constipative Effects of Analgesics.

Woolley (1952) (101) advances the idea that Nalline(R) may be considered an antagonist of morphine which itself acts as an antimetabolite of some as yet unknown metabolic process. His statement: "The observed facts of antagonism between structurally related drugs usually show that one of the pair is much weaker than the other when they are tested singly" tends to be bourne out in this case because Nalline(R) appears to possess one-tenth the strength of morphine. Papavarine has been reported by Schroeder (1933) (102) to counteract the effect of morphine on the pyloric sphincter when used at a ratio of 3:1 in the dog. Demerol also has been reported to diminish the tonic action of morphine on the intestinal tract, according to Yonkman (1944) (103). Morphine (104), which has as one of its major side effects, the property to cause nausea and vomiting, will, in subclinical doses, abolish the effect of apomorphine on the vomiting mechanism. All of these effects appear to be a competition for an activity site of a weaker molecule for a stronger one.

Another factor in this problem is that the intravenous injection of many acridine compounds, as reported by Shaw and Bentley(105,106) will cause a dog under narcosis with 10 mgm./kgm. of morphine to jump up and often run wildly away as if in a panic. The panic reaction may be a part of the morphine complex unmasked by the acriding in view of the report that Nalline(R) by itself will produce dysphoria (107). The acridives themselves are antimetabolites and are used in antibiotic therapy.

That morphine can be changed to apomorphine and produce a highly specialized vomiting center stimulant seems to have a parallel with a a Demerol substitution according to Scott, et al (108). A violent emetic compound can be produced by replacing the ethoxy radical in Demerol with a methyl group. That such chemical changes can cause selective effects on activity centers always encourages one to seek the one compound that will ppoduce analgesia with practically no side effects. After all "Mother Nature" has already accomplished the job by producing individuals who are congenitally indifferent to pain (109, 110, 111, 117, 118).

Summary:

1. The synthetic analgesics alpha acetylmethadol and l-isomethadone have been compared with morphine in rats by means of the Macht Method of measuring intestinal motility; in rabbits by a modification of the Sato modification of the Eddy method of measuring intestinal motility; with a few preliminary experiments in a dog with an isolated intestinal loop; and with a few dogs prepared according to the Jackson method. N-allylnormorphine was also included in these tests as a derivative of morphine which has assumed clinical importance.

2. L-Isomethadone was found to be less constipating than morphine while alpha-acetylmethadol was more constipating by these methods. N-allyl normorphine seemed to possess an effect which was about one-tenth the effect produced by morphine.

3. The rabbit motility method if comparison of drugs for their

intestinal effects was found to be a very sensitive indicator of drug activity.

4. N-allyl normorphine tends to antagonize the constipative effects of opiates, but apparently its own inhibition is substituted for the greater effect of the more potent drugs.

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