no effect in prolonging the incubation period in monkeys. In an appendix to the memoir Major Malone gives reasons for believing that in the period 1925-30 any significant differences in the death rates of the various populations studied were due to one exceptional condition—namely, the method of treatment employed. If no significance can be attached to these differences, it is deducible that no one treatment employed anywhere could be considered better than another.

Hospital Services in the Punjab

The triennial report on the Working of Hospitals and Dispensaries in the Punjab for the years 1929 to 1931, inclusive, reveals that considerable progress has been made towards the ideal of providing one dispensary for every area of 100 square miles, and one for each 30,000 of population. The triennium opened with 964 dispensaries and closed with 1,024, ninety-five of the new ones being situated in rural areas. Colonel D. P. Goil, I.M.S., Inspector-General of Civil Hospitals, Punjab, announces that the scheme of medical relief inaugurated in 1925 is almost complete, only thirteen dispensaries still being required. At the beginning of the triennium there were thirty-two itinerating dispensaries; all have now ceased to function owing to financial difficulties, but the need for them has been much reduced by the steady multiplication of these stationary ones. The taking over by the Province of district and tansil headquarters hospitals has also been arrested by pecuniary considerations, and sixty-seven still await this step in the provincialization of medical treatment. Except in Lahore, hospitals so taken over are supervised by visiting committees. There were large increases in the numbers of patients during the three-year period, and it was estimated that in 1931 more than half the population of the Punjab received medical treatment in the State-public, local fund, and private-aided institutions. There is considerable overcrowding in all hospitals which are surgical centres of repute throughout the cataract season each year, and extra accommodation has to be improvised to meet the rush of patients who come for operative treatment. The figures for the Mayo Hospital at Lahore were the highest since its inauguration. Progress in the development of the Government Hospital for Women and Children in the same city was exceptionally rapid, and the new accommodation provided enabled the admission of a larger number of new cases than had been anticipated. It is no longer necessary, therefore, for Lahore medical students to go to Madras for their obstetrical and gynaecological training. The total number of new cases treated in all hospitals and dispensaries during the triennium was 39,363,000, as compared with 27,868,000 in the previous one and 20,750,000 in 1923 to 1925. The inauguration of the scheme of rural dispensaries increased the attendance of out-patients very considerably, many purdah women making use of them. Diseases of the eye and malaria were the two outstanding reasons for attendance, there having been no grave epidemic of infectious disease in the three years. A new dental hospital was opened at Lahore by the Government, and proved very popular, nearly 18,000 patients having been treated there in 1931.

Egmore Hospital for Women and Children

The Government Hospital for Women and Children at Egmore in Madras was founded in 1844; in the next year, the first complete one of its existence, the number of confinements was 62. Confidence in it slowly grew, and in 1861 the figure reached 1,000, to be doubled thirty years later. Maternity cases alone numbered 3,311 in 1930 and 3,389 in 1931. There is now a large ante-natal department and a children's section. Just before the war

a separate block was erected for teaching purposes solely. This comprised a modern lecture amphitheatre, museum rooms, clinical and research laboratories, a photographic department, and residential accommodation for men and women students. At that time, also, additional wards, an out-patient block, an operation theatre, and spacious quarters for nurses were provided. Although this institution now ranks as one of the largest educational centres in obstetrics and gynaecology for medical students, midwives, and specialists, the retiring superintendent, Lieut.-Colonel C. A. F. Hingston, I.M.S., enumerates in his last report further steps which should be taken as soon as possible to remove certain inconveniences and to increase the efficiency of the hospital. Of these the chief are the establishment of an obstetrical operating theatre, rearrangement of the septic delivery ward so as to obviate any possibilities of cross-infection, the construction of an ante-natal ward and a more suitable ante-natal clinic, and a separate children's department, so that in the present infant welfare section, which includes this department, there may be more room for greater concentration on the physiological requirements of infants suffering from various diseases or needing safeguarding. Colonel Hingston points out that the Egmore Hospital is a provincial institution rather than a Madras city building. The majority of the more serious cases are drawn from almost every district in the Presidency and from the neighbouring Indian States. Within the last few years a successful mothercraft department has been opened, with which is associated a training centre for midwives, who will thus be enabled to disseminate widely the modern ideals of infant feeding and infant care generally. Post-graduate courses for general practitioners have also been a feature of recent years at the Egmore Hospital; they have attended from all parts of India, Burma, the Straits Settlements, Sumatra, Java, and many other parts of the Far East.

CORRESPONDENCE

Substitutes for Morphine and Heroin

SIR,—During the past few years three new synthetic drugs have been manufactured and extensively used on the Continent as substitutes for morphine and heroin. These drugs are being manufactured in Germany, and are marketed under the trade names of dilaudid, dicodid, and eukodol respectively. The clinical literature on these drugs is fairly extensive, but little has been published with regard to their pharmacological actions. A complete survey of the clinical and experimental work on dilaudid is given by Eddy.¹ Articles in the medical press in this country and the United States of America show that considerable interest is felt in this drug. I therefore venture to put forward briefly some evidence which I have myself obtained during the past eighteen months on the pharmacological actions of the drugs dilaudid, dicodid, and eukodol.

Dilaudid is the hydrochloride of dihydromorphine. It is a derivative of morphine, and is manufactured from that substance. Dilaudid is a white amorphous substance, which is freely soluble in water and alcohol, but is insoluble in ether. The aqueous solution has a neutral reaction. The name dilaudid is a registered trade name patented by Knoll, A.-G., of Ludwigshafen-on-the-Rhine. The drug is marketed as a substitute for morphine, and the makers put forward claims for it as an analgesic and as a respiratory sedative.

Dicodid is manufactured by Knoll, A.-G., and is the bitartrate of dihydrocodeinone. Its chemical structure shows it to be a derivative of thebaine. Since, however, it can be obtained from codeine, it must be regarded from the stand-

¹ *Journ. Amer. Med. Assoc.*, 1933, c, 1032.

point of production as a derivative of codeine, and so of morphine. It also is advocated as an analgesic and as a sedative of the respiratory tract.

Eukodol is the hydrochloride of dihydroxycodoinone, and is manufactured, by a patent process, by E. Merck of Darmstadt. It is not a derivative of morphine. It is manufactured from thebaine, and as opium contains but a small quantity of thebaine the amount of *eukodol* manufactured must be very limited. No process is known for the manufacture of thebaine from morphine or codeine. *Eukodol* is used for the same purposes as *dilaudid* and *dicodid*.

The results of my experiments, carried out on laboratory animals, show that:

1. The action of *dilaudid* or *dicodid* (0.5 mg. per kg.) on the intestine, whether the organ be *in situ* or isolated (1/100,000 concentration) is the same, and consists of stimulation of tone and movements (small doses) followed by depression (with large doses—that is, 10 mg. per kg. and 1/20,000). These effects are quite similar to those produced by morphine and heroin, except that heroin has a greater effect on intestinal tonus. The action of *eukodol* differs from this, since it produces little effect in small doses, while large doses produce an increase in tone and movements.

2. *Dilaudid* is the only one of these three drugs which has a marked effect on the pyloric sphincter and the stomach, and in this respect it resembles morphine. *Dilaudid* (0.5 mg. per kg.) produces a well-marked increase in the sphincter movements, which reach a maximum effect after about thirty minutes. These increased movements may continue for a period of two or three hours. At the same time the stomach movements are increased, but the general muscular tone is not altered. The action on the stomach is slow and gradual, and reaches a maximum effect after about forty minutes. These effects are very similar to those of morphine on the same structures. The effects produced by *dicodid* or *eukodol* (1 mg. per kg.) on the movements of the pyloric sphincter and the stomach are so slight as to be negligible. In doses of 5 or 10 mg. per kg. they do, however, slightly increase tone and movements, and in this respect resemble codeine.

3. *Dilaudid* (0.5 mg. per kg.), *dicodid* (0.5 mg. per kg.), and *eukodol* (5 mg. per kg.) markedly increase the tone of the ileo-colic sphincter. In this they resemble morphine and heroin. Larger doses of *eukodol* than of either *dilaudid* or *dicodid* are, however, required to produce these effects. *Dicodid*, which has a weak action on the pyloric sphincter, has, however, a well-marked action on the ileo-colic sphincter. This contraction of the ileo-colic sphincter is very similar to that produced by adrenaline or by stimulation of the sympathetic nerves in the lumbar roots of the spinal column.

4. These three drugs, in doses as small as 0.1 mg. per kg., all produce a most profound effect on the respiration, which becomes slower and deeper, and the general effects resemble those produced by morphine. A toxic dose of any one of these drugs produces a serious progressive depression of the respiratory centre as shown by a marked decrease in rate, depth, and efficiency of respiration. The respiration is finally arrested before the heart is seriously injured.

An interesting observation with regard to the toxicity of *dilaudid* and *dicodid* was made during these experiments. It was found that if a small initial dose such as 0.25 mg. per kg. of one of these drugs was given to an anaesthetized cat, the respiration became slower and deeper. Enormous doses of the drug, such as 20 or 30 mg. per kg., could then be given without causing death or even indeed producing much further effect on the respiration. On the other hand, if an initial dose in excess of the therapeutic dose (that is, 3 mg. per kg.) was given, then the respiration ceased and the animal died. The explanation of this increased tolerance to *dilaudid* or *dicodid* after therapeutic doses is not apparent, but further experiments are now in progress with a view to elucidating this.

An attempt to analyse further the effect on respiration showed that: (1) *Dilaudid*, *dicodid*, and *eukodol* have little or no action on the bronchioles. (2) The sensitivity of the vagus centre is much increased after the administration of

small doses of *dilaudid* (0.25 mg. per kg.). Larger doses (1 mg. per kg.) quickly depress it after a short initial period of increased sensitivity. Similar effects were observed with *dicodid*. *Eukodol*, however, appears to depress the vagus centre even in small doses (0.1 mg. per kg.). It is well known that morphine increases the reflex excitability of the vagus centre; *dilaudid* and *dicodid* therefore resemble morphine in this respect.

Large doses of *dilaudid* and *dicodid* have a well-marked action on the spinal reflexes. One large dose (20 mg. per kg.), or several smaller doses given within a short space of time, will produce twitching of the limbs or the whole body. These twitchings, when severe, are of a convulsive nature, and always can be produced in the conscious, in the pithed, or in the anaesthetized animal. The period during which the reflexes are increased may vary from a few minutes to almost an hour, according to the amount of the drug injected. The twitchings can be abolished immediately by injecting curare or destroying the cord. *Dilaudid* produces these twitchings much more easily than *dicodid*. They are not produced by therapeutic doses, but only when these amounts are grossly exceeded. These effects are similar to those produced by heroin or morphine hydrochloride, which are much more active in this respect. *Eukodol*, even in large doses (30 to 50 mg. per kg.), does not affect the spinal reflexes. This is not what one would expect in view of the fact that *eukodol* is manufactured from thebaine, which is a convulsant.

The effects of therapeutic doses of *dilaudid*, *dicodid*, or *eukodol* on the blood pressure are so slight as to be almost negligible. *Dilaudid* (0.25 to 2.5 mg. per kg.), however, causes a slight slowing of the heart rate, which has little effect upon the blood pressure. The effects produced in mice (0.25 mg. per 20-gram mouse) and rabbits (2.5 mg. per kilo) after the injection of small doses of *dilaudid* and *dicodid* closely resemble those of morphine. Respiration is markedly slower and deeper, and signs of restlessness become manifest. There is paresis of the hind limbs. The gait resembles the hyenoid walk seen in the dog under the influence of morphine. Marked analgesia is present. Recovery takes place in a few hours. Larger doses give rise to the symptoms just described. Later there is an increase in reflexes, which give place to convulsions, and death follows (*dilaudid* 1 mg., *dicodid* 10 mg., per 20-gram mouse).

Eukodol differs from *dilaudid* and *dicodid* in two respects: it does not cause convulsions, and very large doses are needed to cause death. The toxicity of *dilaudid* is much greater than *dicodid*, which is, in turn, greater than that of *eukodol*. The injection of any of these three drugs into mice causes a stiff erection of the tail, which is very similar to that described by Straub for morphine or its esters. Van Leersum¹ believes this to be due to intense tenesmus of the anal and bladder sphincters originating in the medulla and transmitted through the pelvic nerves, while Heinekamp² refers it to stimulation of the spinal cord.

The results of the investigation have shown that the pharmacological actions of *dilaudid*, *dicodid*, and *eukodol* are very similar to morphine, but appear to be much more toxic; smaller amounts of *dilaudid* than of morphine are needed to depress the respiratory centre. *Dicodid*, on the other hand, seems to lie midway between morphine and codeine. *Eukodol* differs from the others in many ways. It has a much weaker action on the movements of the alimentary tract and does not increase spinal reflexes. It has, however, a profound effect upon respiration, which is as marked as that produced by either *dilaudid* or morphine. So far as these investigations go there is no reason to think that any of these drugs are superior from a therapeutic point of view to morphine. Experiments of this type, of course, throw no light on the question of addiction.—I am, etc.,

Pharmacological Laboratory,
Cambridge, May 28th.

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¹ *Journ. Amer. Med. Assoc.*, 1918, lxxi, 783.

² *Journ. Pharm. Exp. Therap.*, 1922, x, 107.