OCCURRENCE IN RODENTS OF REVERSIBLE DRUG-INDUCED OPACITIES OF THE LENS*

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It has been found that several analgesic drugs of the morphine type produce an opacity in the lens when these are administered to rodents (Weinstock, Stewart, and Butterworth, 1958). The opacity is of a transient nature and the eyes resume their normal clear appearance within 2 to 3 hours of the injection of the drug. The duration of many of the other side-effects of these analgesics, such as the characteristic Straub-Hermann reaction (erection of tail) and the dilatation of the pupil in the mouse, is about the same.

There have been a few reports of reversible cataracts produced in small animals, but usually several days or even weeks of daily feeding with the causative substance were necessary before any change in the lens was seen. Robbins (1944) was able to show that chickens and ducklings, that had been fed on a diet that included 0.25 per cent. 2,4-dinitro-phenol, developed lens opacities within 8 hours. The lenses cleared almost entirely 16 hours later, although the birds were still receiving the drug. By injecting this compound intramuscularly in oily solution, Buschke (1947) achieved the same effect in birds within 1½ hours.

Several workers have tried to repeat this action of nitro-phenol in other species, including rats, guinea-pigs, and rabbits, but they were not successful. Bettman (1946) used a special strain of yellow obese mice and even after daily feeding for 4 weeks with dinitro-phenol he obtained an opacity in only 7.5 per cent. of the animals. He was unable to produce it in non-obese mice, albino, grey, or brown. He concluded from other observations that the more rapid development of the effect in birds was due to a difference in their metabolism rather than to a change in the structure of the lens.

Fitzhugh and Buschke (1949) fed rats daily for 3 weeks with 1 per cent. and 2 per cent. beta-tetranol and other derivatives of naphthalene before they were able to detect any opacity in the lens. The effect was not completely reversed 4 months after the drugs had been withdrawn.

It is therefore believed that this is the first description of a reversible lenticular opacity produced by the acute administration of drugs. In no other report was the effect said to be reversed in so short a time as 3 hours.

The return of the lenses to their normal appearance after an opacity has been induced by one of the morphine-like analgesics can be markedly accelerated by injecting the animal with N-allyl-normorphine (Nalorphine), the morphine antagonist. Furthermore, if the injection of Nalorphine precedes that of the analgesic drug, the opacity does not develop.

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Appearance of the Opacity

The typical reaction produced in the mouse by the majority of such analgesic drugs is shown below. Methadone hydrochloride was the drug used in this case, and it was administered subcutaneously, but the effect is similar with other compounds and other routes of administration (Fig. 1).

FIG. 1.—Results of subcutaneous injection of 20 mg. Methadone hydrochloride per kg. body weight, up to 135 min. $\times 15$.

In all cases in which the drug has a mydriatic effect in the mouse eye, the light reflex is first diminished and then cloudiness develops in a crescent shape, usually within the lower portion of the eye, and gradually spreads upwards until the whole area within the pupil has become opaque. The time at which the first signs occur and at which a maximum effect is reached varies with the different drugs. Pethidine, which acts very quickly (within 10 minutes in mice), produces a visible effect on the eye 10 minutes after injection, whereas with morphine very little effect is seen before 25 minutes.

Of some 31 morphine-like compounds tested in this way, the majority begin to have an effect 15 to 20 minutes after subcutaneous injection, and this usually reaches a maximum 15 to 20 minutes later.

The photographs show the whole range of effects obtainable, but often one may only see the stage scored as (++) or even only (+) in a given animal. The incidence of a more marked opacity increases as larger doses of the drug are given.

The Table shows the dose levels of the various analgesic drugs needed to induce an opacity in 50 per cent. of the mice by subcutaneous injection. The ED 50s* for analgesia (Hot-plate method) are given for comparison (Janssen and Jageneau, 1957).

TABLE

Compound	Doses (mg./kg. body weight)	
	ED 50 Opacity	ED 50 Analgesia
Morphine	58.0	5.7
Diacetylmorphine	4.3	2.0
Levorphan	6.0	3.0
Pethidine	43.3	21.1
Methadone	7.8	3.1
Dextromoramide	2.9	0.7

A few of the active drugs that were tested do not have a mydriatic effect in the mouse at the dose levels which give an opacity. In these cases, the formation of the cloudiness usually follows a different pattern and begins as a minute speck in the centre of the small pupil. This gradually spreads, often along the lens suture lines, until it fills completely the whole area that can be seen (Fig. 2).†

FIG. 2.—Appearance of a mouse eye showing opacity without mydriasis. $\times 30$.

* The ED 50 is the dose which produces the effect in 50 per cent. of the mice tested. This value is used because it is impossible to estimate accurately the effective dose in 100 per cent. of cases (*i.e.* ED 100).

† An anoxic dilatation of the pupil occurred while the photograph was being taken because of the way in which the mouse had to be held.

Site of the Opacity

The actual position of the cloudiness on the lens was determined in the following way.

Ten mice were injected subcutaneously with methadone hydrochloride, in a dose of 20 mg./kg. body weight. When an animal had developed a given degree of opacity at a stated time after injection, its eyes were photographed. Immediately afterwards, the mouse was deeply anaesthetized with pentobarbitone sodium 15 mg. intraperitoneally, and the eyes were removed. The lenses were carefully dissected out, and it can be seen in the photographs that the cloudiness which forms on the anterior surface matches closely that seen in the whole eye, both in position and shape (Fig. 3).

FIG. 3.—Results of subcutaneous injection of 20 mg. Methadone hydrochloride per kg. body weight, up to 75 min. with dissected lens. $\times 15$.

Further examination of the enucleated lenses showed that this clouding was a deposit on the surface. Removal of the lens capsule exposed a clear lens substance beneath it; thus showing that the deposition occurred only

on the anterior surface of the lens capsule. It was possible to demonstrate that the opacity does not occur elsewhere in the anterior chamber by means of a slit-lamp microscope. Using this instrument one was able to watch the lens develop this cloudiness soon after injection, while the cornea remained completely transparent.

The deposit could be removed from the capsule by washing the lenses in normal saline, indicating that the phenomenon was reversible even *in vitro*. Because the attachment of the deposit was of such a labile nature, satisfactory histological sections were not achieved.

The exact chemical nature of this deposit is being investigated. When lenses showing an opacity are removed and placed in potassium iodoplatinate solution,* the cloudy portion stains blue, while the rest of the lens remains pink. This indicates that the deposit is an organic base somewhat similar in chemical structure to the original analgesic drug.

Other Species

Although the effect on the lens is seen most readily in mice, it can also be obtained in other laboratory animals, namely guinea-pigs and rats. The opacity could not be produced in 10-day-old chicks injected with methadone, pethidine, or morphine, in doses per body weight that are usually effective in 80 per cent. of the mice. A very slight increase in the amounts injected produced severe toxic symptoms in this species, such as loss of muscular power, respiratory depression, and persistent vomiting, so this investigation was not continued.

The doses required in the rat and guinea-pig were approximately the same as in the mouse on a weight basis. However, with the exception of pethidine, most of the drugs do not dilate the pupil in the rat, unless very large doses in the lethal range are given, so that the effect appears more like that shown in Fig. 2. Also, in the rat, the opacity develops more slowly after subcutaneous injection than in the mouse, and often it is not seen before 50 to 70 minutes. Rats show a greater variation in their response to the action of these drugs on the eye, and when the response occurs the opacity is usually less marked than in the mouse. This may be due to the larger surface area of the lens and greater depth of the anterior chamber in this species.

The pupil is dilated by these drugs in the guinea-pig and the effect is readily visible within 45 minutes of subcutaneous injection of pethidine and methadone, although, in this species also, the degree of the opacity is less marked than in the mouse.

Different strains of all three species have been used and it has been found that the colour of the eyes does not appear to make any difference to the incidence or extent of the opacity, even in albinos.

* (Munier and Macheboef, 1949) alkaloid reagent.

Discussion

A reversible opacity in the lens is described, which is produced by the acute administration of morphine-like analgesic drugs. Unlike any other drug-induced opacity previously reported, this effect is seen 15 to 20 minutes after the injection of these compounds and, whereas they are not reversible, its occurrence can be completely prevented by the simultaneous administration of N-allyl-normorphine (Nalorphine). When the opacity has already developed, subsequent injection of Nalorphine in 1/10th of the dose, causes the effect to disappear in less than a quarter of the normal time. If, however, the same dose is used, the eye becomes quite normal in less than 5 minutes.

The mechanism by which Nalorphine prevents the effect of these drugs on the eye is not known. Nalorphine also antagonizes specifically many of the other actions of analgesics, such as depression of respiration and narcosis, as well as analgesia (Unna, 1943; Woods, 1956).

It has been postulated that analgesic drugs combine with certain specific receptors somewhere in the central nervous system and that this initiates a reaction sequence which results in analgesia (Beckett, Casy, and Harper, 1956). If we now assume that combination with a similar set of receptors is necessary before an opacity can be produced, the mode of action of Nalorphine could be explained by a competition between this agent and the analgesics for these two sets of receptors, so that the normal reaction sequence is prevented in each case. When the exact chemical nature of the deposit on the lens is established, it should be possible to discover whether this active substance is produced locally at the lens surface, or is formed outside the eye and passes into the aqueous humour from the blood stream. One would then be able to obtain more precise information concerning the mode and site of action of this antagonist.

The occurrence of this opacity has the advantage of being readily reproducible. This has enabled us to use it to study the influence of drugs on the dynamics of aqueous humour in rodents. The rate of onset and decline of the effect can be varied by drugs that are known to alter the formation and reabsorption rate of aqueous humour (Weinstock, unpublished observations).

Wikler (1950) found that visual thresholds were elevated to about ten times their original value in morphine addicts but attributed this to the constriction of the pupil which this drug produces in the human subject. Bearing in mind that the anterior chamber is so much deeper in man and that humans are so much more sensitive to the actions of morphine-like drugs, it is unlikely, except in an addict, that sufficient dosage could be given to produce a definite opacity, but enough might be present, as in animals, to bring about a reduction in the light reflex. Therefore, it would be of interest to examine patients receiving these compounds to see whether any

reduction in visual acuity results from the deposition of material on the lens surface as well as from the action on the pupil.

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