expectation. Up to the present we have ascribed this failure to demonstrate a lower testicular temperature to inadequacies in technique, but it is possible, though improbable, that no such differential exists. The improbability is based on the almost invariable thermal gradient between the hot-bodied bird and the cooler environment. Thus, if tropical species of birds have temperatures approximating those of their temperate-zone relatives, the favorable nature of the gradient would be 42–43° C. in the birds (often still higher when they are active) to 29–30° C., the mean annual air temperature.

Because of the failure in the physiological investigations it seemed advisable to re-examine the location of one of the morphological characteristics that might be credited with the hypothetical lowering of the testicular temperature, namely, the air sac system.

In order to obtain an accurate picture of the natural relationships of the visceral organs, the birds were not inverted to the usual position employed in anatomical studies or while being "sexed" during the preparation of scientific skins. Omission of this technique may have been the factor that has obscured the true relationships of testes to air sacs. While in their normal position the air sac systems of the birds used (*Euphagus cyanocephalus*, Brewer's blackbird) were injected with a latex solution.

These studies were continued over two successive seasons of the testicular cycle, and they clearly demonstrated that the testes move a short but important distance downward and backward, so that during the warm spring months while spermatogenesis is in progress *the testes become enveloped between the two dorsal folds of the abdominal air sacs.*

In this as in all other species of Nearctic birds a late spring or summer testicular regression takes place, and the behavior of the organs strongly suggests that the insulating or cooling propensities of the air sacs are not fully adequate to prevent some heat damage, but a sufficient measure of relief is accorded the birds to enable them to reproduce before collapse of gonads takes place.

The entire performance so closely resembles the picture of heat-induced collapse in other animals that it has been deemed advisable to continue similar studies in order to determine whether this similarity is superficial, a result of light changes, or mere coincidence, or whether it is genuine heat effect. It is believed that prolonged but moderate overheating will prove to be a major factor.

References

1. Cowles, R. B. *Amer. Nat.*, 1945, **79**, 160–175.
2. Cowles, R. B., and Burleson, G. L. *Amer. Nat.*, 1945, **79**, 417–435.
3. Riley, G. M. *Soc. Biol. Med.*, 1937, **34**, 331.

Comparison of Some New Analgesic Compounds

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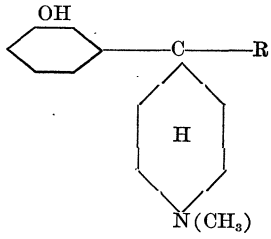
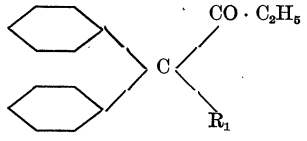
Knowledge of new analgesic agents prepared by German chemists has recently been published by the U. S. Department of Commerce (*4*). A number of these substances possess marked pharmacologic properties. A report on one outstanding member of this group has already been made from this laboratory (*5*). It is, chemically, 1,1-diphenyl-1-(dimethylamino-isopropyl)butanone-2 (German Serial No. 10820). However, other compounds in the series appear to have good possibilities and deserve further study, particularly from a clinical point of view. The following is a brief comparison of six of the compounds with demerol and 10820. As shown by the following structures, three of them are closely related to 10820, and the other three, to demerol. In fact, demerol is identical with 10446 except that it has no OH-group in



(I)

$R = COO \cdot C_2H_5$ [10446]
$= CO \cdot C_2H_5$ [10720]
$= CO \cdot CH_3$ [10726]



(II)

$R_1 = CH_2 \cdot CH(CH_3) \cdot N(CH_3)_2$ [10820]
$= CH_2 \cdot CH_2 \cdot N(CH_3)_2$ [10582]
$= CH_2 \cdot CH_2 \cdot N$ (H) O [10581]
$= CH_2 \cdot CH(CH_3) \cdot N$ (H) [10819]

the metaposition of the benzene ring. The substances other than demerol, designated by their original German numbers, were prepared by Drs. T. P. Carney and E. Rohrmann, of our organic chemical department.

Methods. Analgesic action was determined in rats

[1] Thanks are due Francis W. Israel for technical assistance in this study.

by the method of Haffner (*2*) and in dogs and man by thermal radiation technique (*1, 3*). In rats and dogs the substances were administered by intraperitoneal injection, and in man, by mouth. Effects on circulation, respiration, and salivary (submaxillary) flow (10726). The depressor effects of the diphenyl compounds were less marked.

Cardioinhibition resulted from administration of any of the diphenyl substances, but only one of the demerol group (10720) produced this effect. Cardiac slowing was apparently due to stimulation of the vagal center, since it could be abolished by section of the vagus nerves or atropinization.

Striking differences were observed in the effects on respiration. Stimulation resulted from administration of the esters, whereas depression occurred with the ketones. Whether or not this is a coincidence will depend on further work with more compounds of the same series.

Inhibition of salivary secretion approaching that caused by atropine was noted with the esters. The ketones, however, showed much less effect.

Four new compounds were tested on man along with demerol and 10820. With threshold doses, certain mild side reactions were encountered with all of them. The most frequent symptom was lightheadedness (not true vertigo), the intensity of which appeared to vary with the degree of analgesia. Nausea and vomiting were relatively rare in the doses studied.

TABLE 1

COMPARISON OF THE PHARMACOLOGIC ACTION OF A SERIES OF NEW ANALGESIC AGENTS

Compound No.	$LD_{50} \pm$ S. E. in mice by vein (mg./kg.)	Analgesic action: threshold dose			Action in anesthetized dog by vein				
		Rat (mg./kg.)	Dog (mg./kg.)	Man (mg.)	Dose (mg./kg.)	Blood pressure (mm. Hg)	Heart rate	Respiration (%)	Depression of saliva
Demerol	40.8 ± 1.4	8	10	100–150	1	− 65	Unchanged	+ 110	Marked
10446	85.3 ± 5.8	5	10	80	5	− 60	"	+ 33	"
10720	13.7 ± 1.0	1	2	7.5	1	− 70	Slowed	− 53	Moderate
10726	104.0 ± 5.8	8–16	16		10	Unchanged	Unchanged	Unchanged	Slight
10820	17.3 ± 0.9	1	1	5	2	− 25	Slowed	− 56	"
10582	31.4 ± 2.4	2	4–8	20–30	2	− 40	"	− 33	"
10819	17.8 ± 1.3	2	2	5	1	− 30	"	− 28	"
10581	29.4 ± 2.0	2			1	− 20	"	− 42	"

were measured with standard procedures in dogs under barbiturate anesthesia. In this case, injections were all made intravenously. The median lethal dose in mice by intravenous injection was ascertained for each compound.

Results. Table 1 shows the findings for the various tests. It is obvious that six compounds (10820, 10446, 10582, 10581, 10819, and 10720) are more active analgesically than demerol when the results in rats, dogs, and man are compared. Compound 10446 has the same potency as demerol in dogs, but it is more effective in rats and man. The introduction of an OH-group at metaposition in the benzene nucleus (10446) increases the analgesic action of demerol. The ketone form (10720) is more potent than the ester form (10446). Compound 10726 caused such severe vomiting that it was not tested in man. All the diphenyl derivatives are ketones and have a relatively high potency. No study was made with 10581 in dogs and man due to shortage of material.

Analgesic potency and acute toxicity appear to parallel each other, but the relationship is by no means exact. The effects on blood pressure of anesthetized dogs show marked differences. Considerable and prolonged fall of blood pressure followed injection of the demerol derivatives, with one exception

References

1. ANDREWS, H. L., and WORKMAN, W. *J. Pharm. exp. Therap.*, 1941, **73**, 99.
2. HAFFNER, F. *Dtsch. med. Wschr.*, 1929, **55**, 741.
3. HARDY, J. D., WOLFF, H. G., and GOODELL, H. *J. clin. Invest.*, 1940, **19**, 649.
4. KLEIDERER, E. C., RICE, J. B., CONQUEST, V., and WILLIAMS, J. H. Report No. 981, Office of the Publication Board, Department of Commerce, Washington, D. C.
5. SCOTT, C. C., and CHEN, K. K. *Fed. Proc.*, 1946, **5**, 201; *J. Pharm. exp. Therap.*, 1946, **87**, 63.

Scanning Science—

The Commissioner of Labor has submitted to the House of Representatives a plan for the organization of a permanent Census Bureau in Washington. The Director of the Census will be paid $6000 a year, the Assistant Director $4000. In addition there are to be three clerks and five statisticians. It is provided that a general census shall be taken April 15, 1900, and every ten years thereafter.

—18 December 1896