Proceedings of the Sixth International Congress of Pharmacology

General Editors: J. TUOMISTO & M. K. PAASONEN

Volume 3

CENTRAL NERVOUS SYSTEM AND BEHAVIOURAL PHARMACOLOGY

Editor:

M. AIRAKSINEN

Proceedings of the Sixth International Congress of Pharmacology

VOLUME 3

CNS AND BEHAVIOURAL PHARMACOLOGY

Volume Editor

M. AIRAKSINEN
University of Kuopio

PERGAMON PRESS

OXFORD . NEW YORK . TORONTO . SYDNEY . BRAUNSCHWEIG

Pergamon Press Offices:

U. K.	Pergamon Press Ltd., Headington Hill Hall, Oxford OX3 0BW, England
U. S. A.	Pergamon Press Inc., Maxwell House, Fairview Park, Elmsford, New York 10523, U.S.A.
CANADA	Pergamon of Canada, Ltd., 207 Queen's Quay West, Toronto 1, Canada
AUSTRALIA	Pergamon Press (Aust.) Pty. Ltd., 19a Boundary Street, Rushcutters Bay, N.S.W. 2011, Australia
FRANCE	Pergamon Press SARL, 24 rue des Ecoles, 75240 Paris, Cedex 05, France
WEST GERMANY	Pergamon Press GMbH, 3300 Braunschweig, Postfach 2923, Burgplatz 1, West Germany

Library of Congress Cataloging in Publication Data

International Congress of Pharmacology, 6th, Helsinki, 1975.
Central nervous system and behavioural pharmacology.
(Proceedings of the Sixth International Congress of Pharmacology; v. 3)
Bibliography: p.
Includes index.
1. Psychopharmacology—Congresses. 2. Central nervous system—Congresses.
I. Airaksinen, M. II. Title.
RM21.I58 1975 vol. 3 [RM315] 615'.1'08s [615'.78] 75-33071

ISBN (Volume 3) 0 08 020541 0
ISBN (6-Volume set) 0 08 020458 9

Printed in Finland by Forssan Kirjapaino Oy, Forssa.

List of authors

AHTEE, Liisa	Department of Pharmacology, School of Pharmacy, University of Helsinki, 00170 Helsinki 17, Finland
ALFREDSSON, G.	Division of Neuropsychopharmacology, Department of Pharmacology, Karolinska Institutet, S-10401 Stockholm, Sweden
ARIMURA, A.	Department of Medicine, Tulane University School of Medicine, New Orleans, Louisiana 70112, USA
ASHCROFT, G. W.	MRC Brain Metabolism Unit, University Department of Pharmacology, George Square, Edinburgh EH8 9ZJ, United Kingdom
BANGHAM, A. D.	Biophysics Unit, Agricultural Research Council, Institute of Animal Physiology, Babraham, Cambridge, United Kingdom
BARANY, E. H.	Department of Medical Pharmacology, Uppsala University, S-75123 Uppsala, Sweden
BASS, N. N.	Department of Neurology, University of Virginia School of Medicine, Charlottesville, Virginia, USA
BERTILSSON, L.	Department of Clinical Pharmacology, Huddinge Hospital, S-141 86 Huddinge, Sweden
BJERKENSTEDT, L.	Division of Neuropsychopharmacology, Department of Pharmacology, Karolinska Institutet, S-10401 Stockholm, Sweden
BOHUS, B.	Rudolf Magnus Institute for Pharmacology, Medical Faculty, University of Utrecht, Utrecht, the Netherlands
BOISSIER, J. R.	Unité de Neuropsychopharmacologie de l'INSERM, 2 rue d'Alésia, 75014 Paris, France
BORRELL, J.	Departments of Endocrinology and Pharmacology of the University of Milan, 20129 Milan, Italy
BUROV, Yu. V.	Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow 125315, USSR
COOK, L.	Department of Pharmacology, Research Division Hoffman-La Roche Inc., Nutley, New Jersey 07110, USA
de VELLIS, J.	UCLA School of Medicine, Los Angeles, California 90024, USA
de WIED, D.	Rudolf Magnus Institute for Pharmacology, Medical Faculty, University of Utrecht, Utrecht, the Netherlands
DEWS, P. B.	Laboratory of Psychobiology, Harvard Medical School, Boston, Massachusetts 02115, USA
DOW, R. C.	MRC Brain Metabolism Unit, University Department of Pharmacology, George Square, Edinburgh EH8 9JZ, United Kingdom
EBSTEIN, R.	Department of Psychiatry, New York University Medical Center, New York, New York 10016, USA
EFENDIC, S.	Department of Endocrinology and Metabolism, Karolinska Hospital, S-10401 Stockholm, Sweden
ENEROTH, P.	Division of Neuropsychopharmacology, Department of Pharmacology, Karolinska Institutet, S-10401 Stockholm, Sweden
FRASER, H.	Department of Surgery, University of Dundee, Dundee, United Kingdom
FUXE, K.	Department of Histology, Karolinska Institutet, S-10401 Stockholm, Sweden
FYRÖ, B.	Division of Neuropsychopharmacology, Department of Pharmacology, Karolinska Institutet, S-10401 Stockholm, Sweden

GISPEN, W. H.	Rudolf Magnus Institute for Pharmacology, Medical Faculty, University of Utrecht, Utrecht, the Netherlands
GOLDSTEIN, Dora B.	Department of Pharmacology, Stanford University School of Medicine, Stanford, California 94305, USA
GOLDSTEIN, M.	Department of Psychiatry, New York University Medical Center, New York, New York 10016, USA
GOODWIN, F. K.	Intramural Research Program, NIMH, Bethesda, Maryland 20014, USA
GOTTFRIES, C.-G.	University of Umeå, Umeå, Sweden
GROSS, M. M.	Division of Alcoholism, Department of Psychiatry, Downstate Medical Center, State University of New York, Brooklyn, New York 11203, USA
HARTHOORN, A. M.	Transvaal Nature Conservation Division, Pretoria 0001, South Africa
HOFFMEISTER, F.	Institut für Pharmakologie der Bayer AG, D-5600 Wuppertal 1, Federal Republic of Germany
HÄRNRYD, C.	Division of Neuropsychopharmacology, Department of Pharmacology, Karolinska Institutet, S-10401 Stockholm, Sweden
HÖKFELT, T.	Department of Histology, Karolinska Institutet, S-10401 Stockholm, Sweden
JEFFCOATE, S.	Department of Metabolic Diseases, St. Thomas's Hospital, London, United Kingdom
JIMERSON, D.	Intramural Research Program, NIMH, Bethesda, Maryland 20014, USA
JOHANSSON, Barbro	Department of Neurology, University of Göteborg, Göteborg, Sweden
JOHANSSON, O.	Department of Histology, Karolinska Institutet, S-10401 Stockholm, Sweden
KAMBERI, I. A.	Institute for Research in Human Reproduction and Reproductive Biology, Teheran, Iran
KASTIN, A. J.	Experimental Therapy Division, Abbott Laboratories, North Chicago, Illinois, USA
KELLEHER, R. T.	New England Regional Primate Research Center, Southborough, Massachusetts 01772, USA
KORF, J.	Department of Biological Psychiatry, Psychiatric University Clinic, Gronigen, the Netherlands
KOZLOVSKAYA, M. M.	Department of Pharmacology, Pavlov Medical Institute, Leningrad, P-98, 197089, USSR
LeBLANC, A. E.	Addiction Research Foundation, Toronto 4, Ontario, Canada
LUFT, R.	Department of Endocrinology and Metabolism, Karolinska Hospital, S-10401 Stockholm, Sweden
LUNDBORG, P.	Department of Pharmacology, University of Göteborg, Göteborg, Sweden
LÖFSTRÖM, A.	Department of Histology, Karolinska Institutet, S-10401 Stockholm, Sweden
MARTINI, L.	Departments of Endocrinology and Pharmacology of the University of Milan, 20129 Milan, Italy
McCLEARN, G. E.	Institute of Behavioral Genetics, University of Colorado, Boulder, Colorado 80302, USA
MORSE, W. H.	Laboratory of Psychobiology, Department of Psychiatry, Harvard Medical School, Boston, Massachusetts 02115, USA
MÜLLER, E. E.	Department of Experimental Endocrinology, School of Medicine, University of Milan, 20129 Milan, Italy
PARK, D.	Department of Psychiatry, New York University Medical Center, New York, New York 10016, USA
PIVA, F.	Department of Endocrinology and Pharmacology of the University of Milan, 20129 Milan, Italy

Continued on p. X

Preface

The International Union of Pharmacology (IUPHAR) held the Sixth International Congress of Pharmacology in Helsinki, Finland on 20–25 July 1975. The scientific programme was organised with the help of the International and Scandinavian Advisory Boards and it consisted of 15 invited lectures, 20 symposia, 5 seminars on methods, and volunteer papers, some of them as poster demonstrations. Altogether 1580 communications were delivered by the 2.600 active participants attending the Congress.

The texts of the invited lectures and symposia have been included in the Proceedings of the Congress. It is readily noticeable that all the major areas of pharmacology, including clinical pharmacology and toxicology, are well represented. Special attention has been paid to several interdisciplinary areas which are on the frontiers of pharmacology and have connections with physiology, biochemistry and endocrinology. Many of the topics are of special interest to internists, psychiatrists, neurologists and anaesthesiologists. Chapters on the abuse of alcohol, new teaching methods and the conservation of wild animals reflect the wide scope of the Congress.

One can hardly imagine any other Congress Proceedings where more world-famous authors representing pharmacology and the related sciences have reported the most recent developments in their special fields. The invited lectures give a particularly clear introductions to the areas in question, even for those previously unfamiliar with them.

For the first time the Proceedings of an International Pharmacology Congress have been produced by the photo offset-litho process. This method was chosen in order to publish the volumes in the shortest possible time. It clearly demands the emphasis be placed upon the scientific content of the volumes, possibly at the expense of retaining some infelicities of style or presentation.

We are convinced that these Proceedings present a unique opportunity to keep abreast of the latest developments in pharmacology and related areas of research. Our sincere thanks are due to the authors, the members of the advisory boards and our colleagues of the Programme Committee for making the scientific programme of the Congress so successful and the publication of the Proceedings possible.

The Editors

PLOTNIKOFF, N. P.	Endocrinology Section, Veterans Administration Hospital, New Orleans, Louisiana, USA
POST, R. M.	Intramural Research Program, NIMH, Bethesda, Maryland 20014, USA
PULLAR, I. A.	Lilly Research Centre Ltd., Erl Wood Manor, Windlesham, Surrey, United Kingdom
ROOS, B.-E.	Department of Psychiatry, University Hospital, University of Uppsala, S-75014 Uppsala, Sweden
SEDVALL, K.	Division of Neuropsychopharmacology, Department of Pharmacology, Karolinska Institutet, S-10401 Stockholm, Sweden
SEPINWALL, J.	Department of Pharmacology, Research Division Hoffmann-La Roche Inc., Nutley, New Jersey 07110, USA
SIMON, P.	Unité de Neuropsychopharmacologie de l'INSERM, 2 rue d'Alésia, 75014 Paris, France
SOUBRIE, P.	Unité de Neuropsychopharmacologie de l'INSERM, 2 rue d'Alésia, 75014 Paris, France
SOURKES, T. L.	Department of Psychiatry, 1033 Pine Avenue West, Montreal, Quebec, Canada H3A 1A1
SPIRTES, M. A.	Departments of Pharmacology and Medicine, Tulane University School of Medicine, New Orleans, Louisiana 70112, USA
SWAHN, C.-G.	Division of Neuropsychopharmacology, Department of Pharmacology, Karolinska Institutet, S-10401 Stockholm, Sweden
URBAN, I.	Rudolf Magnus Institute for Pharmacology, Medical Faculty, University of Utrecht, Utrecht, the Netherlands
VALDMAN, A. V.	Department of Pharmacology, Pavlov Medical Institute, Leningrad, P-98, 197089, USSR
Van LOON, G. R.	Departments of Medicine and Physiology, Room 6265, Medical Sciences Building, University of Toronto, Toronto, Ontario M5S 1A8, Canada
van PRAAG, H. M.	Department of Biological Psychiatry, Psychiatric University Clinic, Groningen, the Netherlands
van WIMERSMA GREIDANUS, Tj. B.	Rudolf Magnus Institute for Pharmacology, Medical Faculty, University of Utrecht, Utrecht, the Netherlands
WALLGREN, H.	Department of Zoology, Division for Physiology, University of Helsinki, 00100 Helsinki Finland
WIESEL, F.-A.	Division of Neuropsychopharmacology, Department of Pharmacology, Karolinska Institutet, S-10401 Stockholm, Sweden
WILK, S.	Department of Pharmacology, Mount Sinai School of Medicine of the City University of New York, New York, New York 10029, USA
WINGER, G.	Department of Pharmacology, University of Michigan Medical School, Ann Arbor, Michigan 48104, USA
WODE-HELGODT, B.	Division of Neuropsychopharmacology, Department of Pharmacology, Karolinska Institutet, S-10401 Stockholm, Sweden
WOODS, J. H.	Department of Pharmacology, University of Michigan Medical School, Ann Arbor, Michigan 48104, USA
YATES, C. M.	MRC Brain Metabolism Unit, University Department of Pharmacology, George Square, Edinburgh EH8 9JZ, United Kingdom
ZAKUSOV, V. V.	Institute of Pharmacology, Academy of Medical Sciences of the USSR, 125315 Moscow, USSR
ZVARTAU, E. E.	Department of Pharmacology, Pavlov Medical Institute, Leningrad, P-98, 197089, USSR
ÅSBERG, Marie	Department of Psychiatry, Karolinska Hospital, S-10401 Stockholm, Sweden

Contents

Invited lectures

PSYCHOPHARMACOLOGY AND CONSERVATION

A.M. Harthoorn, Transvaal Nature Conservation Division, Pretoria, South Africa.

Introduction

The main theme of this paper is the application of psychopharmacology to conservation practice, principally that branch associated with the capture and relocation of wild ungulates. This particular aspect includes the chemical restraint of free-living wild animals and the alleviation of fear, anxiety and depression during captivity. The other themes are the value of wild animals as models for essential normal behaviour, and the allied theme of the necessity of investigating wild animals, African in particular, while they are still available.

One of the problems inherent in the screening of drugs with the use of test animals is the paucity of animals that are essentially normal. We tend to think of abnormality as a divergence by some individuals from the usual pattern. This pattern in itself may be grossly abnormal by biological standards due to conditioning, feeding, or selective breeding. Perhaps we should look for the normal among animals that have had the least contact with man, man-manipulated environment, or with domestic stock.

A possibly fruitful line of investigation is the extent to which wild animals may be considered or used as models of normal behaviour. When drugs are screened for various pharmacological properties, we are dealing with a brand of pharmacology in which behaviour is the substrate. Many of the compounds that are used in clinical medicine are evolved to control deviations from accepted modes of behaviour in man. Yet the animals in which they are screened are not only very different from man, but perhaps even more different from the animal in its natural state. As such the latter may be considered as an intact unrestrained organism as compared to tests on the more rigid isolated subject under laboratory conditions.

Wild animals are those that are free-living, and have come into minimal contact with man. Almost any regular contact will alter regular behaviour pattern, or cause disturbance and stresses. Fencing of a game reserve or national park may induce migratory animals to pile up against the fence and die in their thousands. The survivors will undergo a change in their behaviour pattern but many decades may pass before they even start to build up to their previous numbers, and may in fact fail to do so. Something in the natural animal as a local race has been destroyed.

More demonstrably a captive animal is different from his wild

counterpart or,rather,different from what he was before capture. A captured wild animal may be immobilised with a much smaller dose,usually about 2/3rds,than that needed for the original capture. It is difficult to know what has been changed except the motivation. The free animal is motivated to escape. Once captured,and attempts to escape have proved futile,the psychological drive to resist the drug effects is lost,and provides an example of how a change may be brought about in the dose-effect curve of a drug with a change in drive or motivation.

Other explanations of this phenomenon may be valid. The animal may have suffered stresses and adrenal exhaustion. It may have lost weight. Its food intake may have been reduced or the protein content lowered. Again,the genetic determination of the phenotype may be able to manifest itself under certain effects that may become evident only in the appropriate environment and under special circumstances. We accept that behaviour is the outcome of the interaction of genetic and environmental factors or forces. If we change the environment,then the behaviour is modified. It is the behaviour that is influenced by drug action as much as the actual physiological mechanisms,and an extraordinary resistance can be manifested by animals intent on escape whether to tranquillisers,anaesthetics; and even incapacitation from bullet wounds.

The foregoing is perhaps more acceptable in the light of well-known and generally accepted difference in drug effect in man in relation to mood,suggestion and indeed personality. Also for that matter in the difference in the effect of drug toxicity according to whether this is administered during the day or night.

Factors affecting drug dosage

Dosage rate

The earlier standard combinations of morphinomimetic compounds and tranquillisers that still enjoy extensive use may be summarised as follows:

etorphine-acetylpromazine	for large animals
etorphine-trimeprazine	for small animals
fentanyl-azaperone	for medium-sized animals

Examples for the larger wild animals are the following:

TABLE 1

Dosage rates and antagonist - white (square-lipped) rhinoceros[8].

weight range (kg)	etorphine (mg)	acetylpromazine (mg)	hyoscine (mg)	diprenorphine (mg)
700 - 1400	0.5 - 1.75	1.0 - 3.5	25 - 50	2 - 3
1600 - 2000	1.5 - 2.0	3.0 - 4.0	25 - 50	4 - 6

TABLE 2

Dosage rates for adult African elephant[4].

no. tested	etorphine (mg)	induction time (mins)	antidote (mg)	recovery time (mins)
30	8.9	13.6	diprenorphine 6.1	4.4
11	8.0	15.7	cyprenorphine 20.1	2.7

Facilitation and behaviour

The excited animal needs a large drug dose to become tractable. Relatively small drug doses may be effective if the animal is unaware that it has been injected. Once the animal becomes disturbed, substantially larger doses may fail to induce it to stop, and there appears to be only facilitation with absence of depression.

Here also there are complicating factors. A running animal must be followed and this in itself provides a stimulus. The arousal threshold for this stimulus is lowered as noise creates a situation where it must be apparent to the animal that it is being hunted, thus reinforcing the stimulus. This tendency for some animals, in particular antelope such as eland and oryx to run has created many problems. Primarily the three problems a) once running, the injected dose is unlikely to induce restraint, b) if followed, the animal is almost certain to become hyperthermic, and c) other factors such as adrenaline discharge, stress, and fall in blood pH, will militate against its survival (Figs 1 & 2).

Fig. 1. Lactate levels in eland following exercise.

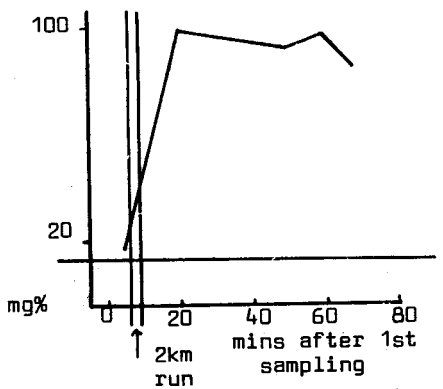
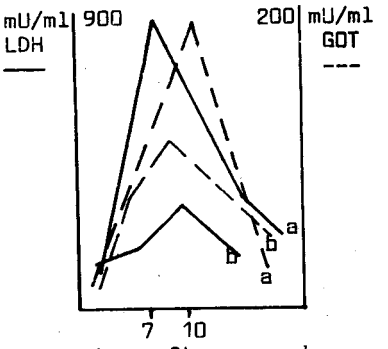


Fig. 2. Blood enzyme levels. a = untreated b = treated



Injected animals usually leave the herd, thus greatly facilitating identification which may otherwise be difficult, especially if the projectile syringe falls out, and may turn away from the general direction of the herd movement and towards the captors. There is a tendency to seek cover, which may be induced at least partially by photophobia due to mydriasis. Cycloplegia may likewise make animals feel uneasy in the open and seek cover to hide.

The trend of movement towards cover is a reduced problem in that the animal loses the ability to move quietly through undergrowth, and moves noisily through rather than around bushes, continues to walk, stumble, and describes an erratic path, sometimes emerging at the point of entry of a copice. This erratic behaviour and tendency to keep walking is a highly reassuring factor when dealing with animals such as the buffalo (Syncerus caffer) which has a reputation for lying concealed until the hunter or tracker is within range of a rapid rush, and which when annoyed, is most assiduous in his pursuit through terrain which for man may be difficult to negotiate.

Conditioning and drug affected behaviour

An injected animal that is ambulant may become habituated to a stimulus,with a rise in the threshold for arousal. A simple demonstration is to drive around in wide but diminishing circles; taking care not to induce a response until the arousal response diminishes and is eventually lost. Under these circumstances a very close approach may be made that may permit either further injection or manual capture. This may be described as a repetition of biologically insignificant stimuli so that the conditioning of the animal to flight and fright is satiated,and the drive dimension is altered.

Curiosity in animals may be used to attract. Many antelope and deer are essentially curious in nature and hunters have made use of this characteristic to attract animals to within range by waving pieces of bunting. Such curiosity will bring them only to within a certain range,a distance when curiosity is balanced by fear. When an animal has been injected there is a marked elevation of the threshold for aversion while the curiosity is left unaltered,perhaps increased. The promazines appear to be effective in this regard,and also etorphine. The early physiological experiments with etorphine on sheep indicated a marked reduction of fear and concomitant rise in apparent curiosity. The change in behaviour of animals under drug influence may be remarkable and such change rather than the drug effect itself is often conducive to capture.

The paradoxical error of certain animals such as rhinoceros to approach a bush vehicle which is normally an aversion object is referred to later. More curious still is the behaviour trait exhibited by animals trying to force their way over or through obstacles they would normally circumvent,jump over,negotiate,or avoid. Rhinoceros and other animals have become stuck in thick bush after repeated attempts to force their way through and have been captured in this position (Plate 1). On reversal of the narcotic moeity of the drug mixture,the animal usually backs out of its own accord! Giraffe have similarly been captured when they have stopped because one hind leg was held by a low bush (Plate 2)

Plate 1

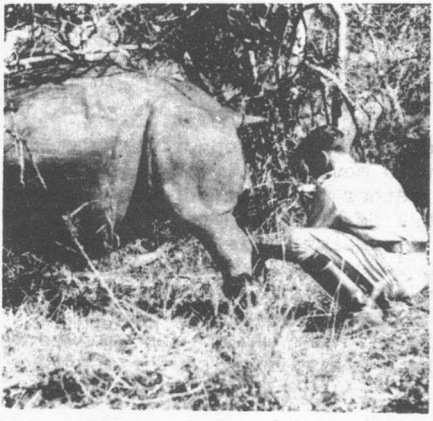
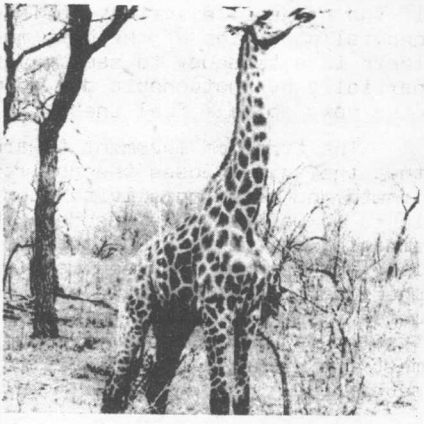


Plate 2



and zebra have stopped behind no greater obstacle than a small fallen tree (Plate 3).

Circling is a marked trait by animals apparently believing they are moving in a straight line from the scene of injection and disturbance. This was typically shown by a mature bull elephant which walked three times past our LandRover while describing a circle several miles in diameter to come to rest close to the place where he was injected (Plate 4).

Plate 3

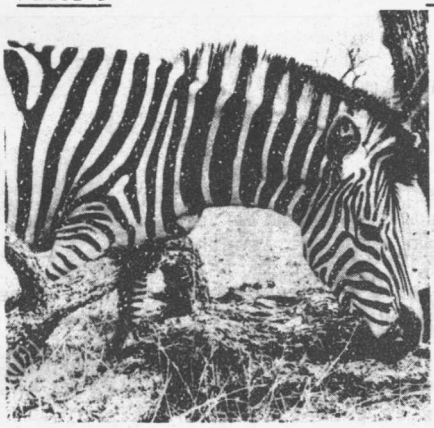
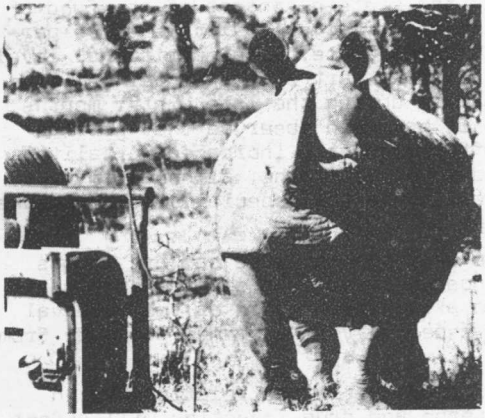


Plate 4

Discrimination and habituation

This curiosity and suppression of avoidance behaviour induces the injected animal to approach normally aversion objects. It appears that the action of certain drugs used for capture is able to influence discrimination or recognition. Numbers of wild animals that have received sub-immobilising doses have been caught in this way, being inclined to approach an immobile human figure or a bush vehicle until they could be seized. Whereas rhinoceros could not be caught in this way, the inclination to approach by injected animals as illustrated in Plate 5 facilitates capture.

Plate 5



The rhinoceros depicted had been injected with etorphine-hyoscine. More often this type of approach has been noted in antelope injected with etorphine-acetylpromazine, and it was first observed in rhinoceros under diethylthiambutene-chlorpromazine-hyoscine. It may be significant to add that this behaviour is noted in animals who have received light dosage rates, insufficient to immobilise, rather than those that were under the influence of neurotoxic or ataxic doses. On other occasions and with other

drug combinations,the animals keep responding to small stimuli even though they appear sedated or even ataxic.

One of the more important aspects,therefore,of chemical restraint is to investigate compounds that appear to lower the significance level for wild animals of a wide range of sensory stimuli,or to potentiate the rate of habituation. Such compounds to be used with others for capture,and on their own during acclimatisation of captured animals to captive conditions.

TABLE 3

Diazepam for relocation[10].

no. transported	sex	weight (kg)	initial dose (mg)	total (mg/kg)	onset of effect (mins)
16	M	14.2	24.5	2.03	48
13	F	15.7	28.1	1.74	19

It is evident that animals suffer from a condition that is analogous to hopelessness in man where the will to survive is lost or impaired. It is well known that the length of time that a tame rat will swim can be greatly reduced if the vibrissae or whiskers are removed. Once this is done,they give up and drown as indeed to their wild counterparts[12]. Many species of wild animal are almost impossible to keep in captivity. Klipspringers are likely to die if picked up,even if tame and kept in a garden or house. The mechanism of such deaths does not really relate to the more commonly observed continuous or excessive adrenergic discharge.

Nutritional factors

A not inconsiderable problem inherent in working with animals in their natural environment is the lack of standard conditions, and the presence of numbers of variable factors that may influence the drug effects.

Foremost among these is the nutritional state. It is generally accepted that relatively small changes in the state of nutrition may have considerable impact on the effects of drugs on behaviour. This is particularly relevant to deficiency in dietary protein,which is known to raise the toxicity of certain poisons. There are large variations in the protein content of the food of wild herbivores in Africa from relatively high levels of 15 percent shortly after new growth takes place,to malnutritional levels of below 1 percent during the latter part of the winter-cum-dry season. This ensures that animals during the late winter months are often in poor condition. It has been observed that giraffe captured during this time,suffer a greatly increased mortality as compared to those captured in other months; although in fact relocation was a further stressing factor,especially if undertaken during the stress period (Fig. 3).

When succinylcholine was used for antelope capture it was generally accepted that the dosage rate for a species in a particular area had to be revised after every month or two interval in the immobilising work,and especially if a change was made from one location to another.

On a smaller scale,the difference in the relationship in time between the grazing patterns and drug injection will affect