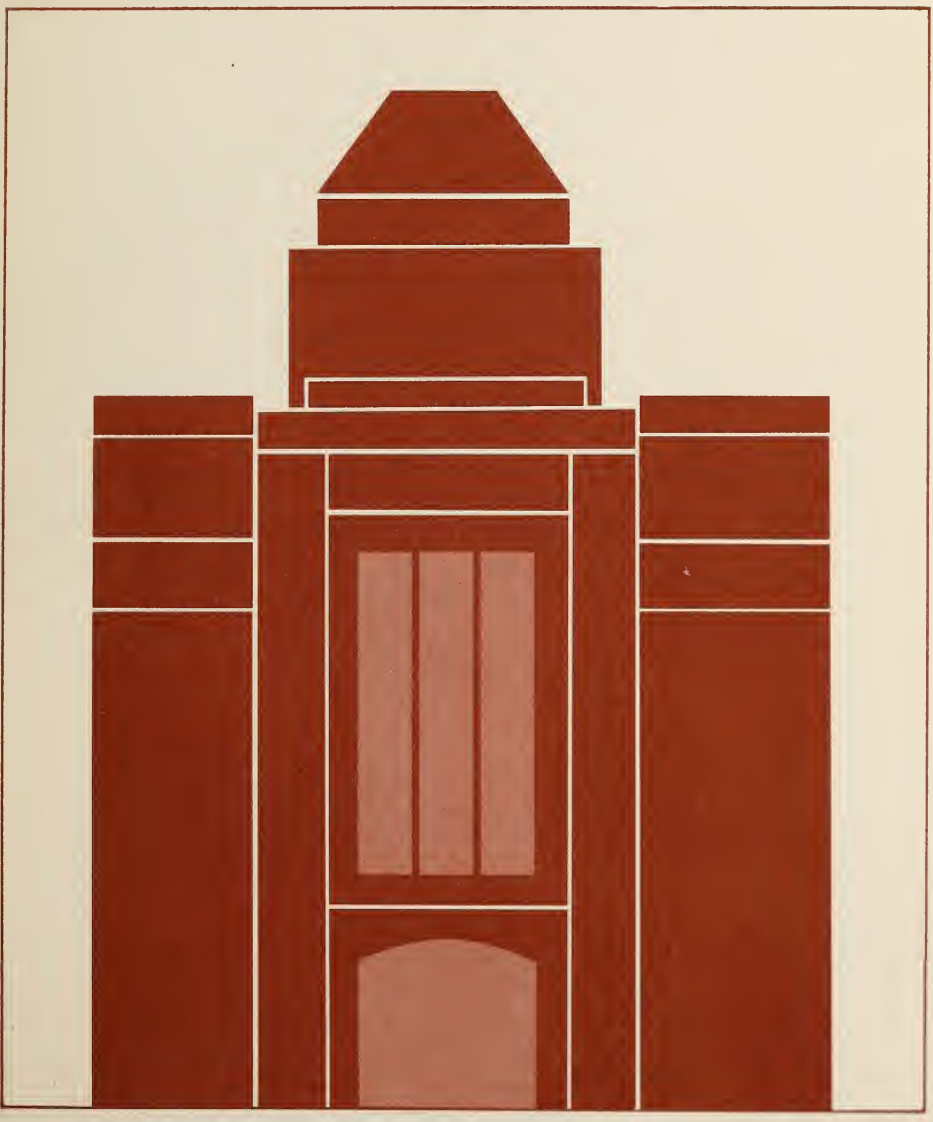
Annotated Bibliography of Papers From the Addiction Research Center 1935-1975



National Institute on Drug Abuse
U.S. Department of Health, Education, and Welfare
Public Health Service
Alcohol, Drug Abuse, and Mental Health Administration

ANNOTATED BIBLIOGRAPHY

NIDA ADDICTION RESEARCH CENTER
LEXINGTON, KENTUCKY

1976

1. BELL, J. A., MARTIN, W. R., SLOAN, J. W. and BUCHWALD, W. F. The effect of L-tryptophan on spinal cord C-fiber reflexes. *Journal of Pharmacology and Experimental Therapeutics* 196: 373-379 (1976).

   C-fiber reflexes were recorded from an ipsilateral S_1 ventral root in the acute decerebrate spinal (T_{10}) cat after stimulation of the superficial peroneal nerve. L-Tryptophan, infused in a dose of 150 mg/kg, increased the C-fiber reflex to 210% (S.E.M. ± 30.1%) of control. This effect was antagonized by cyproheptadine, 0.5 mg/kg. L-Tryptophan increased the C-fiber reflex to 176% (S.E.M. ± 13.0%) of control after *p*-chlorophenylalanine pretreatment. Pretreatment of the cats with the decarboxylase inhibitor α-methyldopa, 100 mg/kg, 30 minutes before infusion, antagonized the facilitatory effects of L-tryptophan. L-Tryptophan, 150 mg/kg, had no effect on the monosynaptic or short latency polysynaptic reflexes. 5-Hydroxytryptophan, 20 mg/kg, had erratic effects on the C-fiber reflex producing both facilitation and depression which were not statistically significant. The recovery of tryptamine from brain perfusates, after perfusion of the anterior cerebellum and pons, with a modified Gaddum push-pull cannula, decreased across time. L-Tryptophan caused a slight increase in tryptamine release which was not statistically significant, whereas in cats pretreated with *p*-chlorophenylalanine, a significant increase in tryptamine release was seen.

2. CLARK, S. C., JASINSKI, D. R., PEVNICK, J. S. and GRIFFITH, J. D. Azidomorphine: Subjective effects and suppression of morphine abstinence. *Clinical Pharmacology and Therapeutics* 19: 295-299 (1976).

   In man, azidomorphine, a new morphine congener, constricted pupils, produced morphine-like subjective effects and euphoria, and suppressed the morphine abstinence syndrome. Azidomorphine was 10 to 50 times as potent as morphine. It is concluded that in man azidomorphine is a typical morphine-like drug.

3. CONE, E. J. General procedure for the isolation and identification of 6-α- and 6-β-hydroxy metabolites of narcotic agonists and antagonists with a hydromorphone structure. *Journal of Chromatography* 129: 355-361 (1976).

   In order to aid in the elucidation of the metabolism of drugs containing the hydromorphone structure, a method is described for isolation from urine, separation and identification of the 6-α- and 6-β-hydroxy metabolites. The samples were acid-hydrolyzed, extracted, and separated by thin-layer chromatography. The zone containing the hydroxy metabolites was removed and the compounds were re-extracted and analyzed by gas-liquid chromatography (GLC). Silylation of the extract was necessary in most cases for optimum GLC resolution of the α- and β-hydroxy epimers.

   To demonstrate application of this method, the urine of guinea-pigs and rats which had received a single 40-mg dose of naloxone subcutaneously was analyzed. Analysis indicated a α/β ratio of 0.41 for the guinea-pig. In contrast, the amount of 6-α-naloxol found in the urine of the rat was negligible in comparison with the 6-β-hydroxy metabolite, indicating a species difference in the stereospecificity of the drug-metabolizing enzyme.

4. GILBERT, P. E. and MARTIN, W. R. The effects of morphine- and nalorphine-like drugs in the nondependent, morphine-dependent and cyclazocine-dependent chronic spinal dog. *Journal of Pharmacology and Experimental Therapeutics* 198: 66-82 (1976).

A series of morphine-like and nalorphine-like drugs were studied in the nondependent, morphine-dependent and cyclazocine-dependent chronic spinal dog. In the nondependent dog, three profiles of activity were found which could be utilized to distinguish between morphine, WIN 35,197-2 and cyclazocine. Propiram, a prototypic partial agonist of the morphine type, produced morphine-like effects in nondependent dogs and both precipitated and suppressed abstinence in morphine-dependent dogs. WIN 35,197-2, a strong agonist in the guinea-pig ileum which has been shown to be resistant to antagonism by naloxone, neither precipitated nor suppressed morphine abstinence but suppressed cyclazocine abstinence. In the nondependent dog, it depressed the flexor reflex but not skin twitch reflex. Cyclazocine altered reflex activity much like WIN 35,197-2 but produced tachycardia, tachypnea, mydriasis and canine delirium. The morphine and cyclazocine precipitated and withdrawal abstinence syndromes were qualitatively different. Twenty times as much naltrexone was needed to precipitate abstinence in cyclazocine-dependent dogs as was needed to precipitate abstinence in morphine-dependent dogs. Nalorphine both precipitated and suppressed cyclazocine abstinence and appeared to be a partial agonist of the nalorphine-type. Morphine suppressed the cyclazocine abstinence syndrome. Cross-tolerance was not observed in ketocyclazocine-dependent dogs. These data are consistent with the hypothesis that there are strong and partial agonists of the μ and κ types, and further, that physical dependence on morphine and cyclazocine is mediated through different receptors. WIN 35,197-2 appears to be a pure strong agonist of the κ type. Cyclazocine is a μ antagonist and mixed κ and σ agonist.

5. GILBERT, P. E. and MARTIN, W. R. Sigma effects of nalorphine in the chronic spinal dog. *Drug and Alcohol Dependence* 1: 373-376 (1976).

The effects of graded doses of nalorphine and morphine were studied in nondependent chronic spinal dogs. Morphine and low doses of nalorphine produced behavioral changes characterized by indifference, whereas the largest dose of nalorphine produced canine delirium indistinguishable from that produced by SKF-10,047 or cyclazocine. Nalorphine depressed the flexor reflex; however, a plateau was observed. The data suggest that nalorphine is a partial agonist of the κ type and a σ agonist in addition to being a competitive antagonist at the μ receptor, and further, that the dysphoric and hallucinogenic effects of nalorphine-like drugs are due to their σ activity.

6. GRIFFITH, J. D. Structure-activity relationships of several amphetamine-like drugs in man. In: Ellinwood, E. H. Jr. and Kilbey, M. M. (eds.): *Cocaine and other stimulants*. pp. 705-715. New York: Plenum 1976.

7. JASINSKI, D. R., PEVNICK, J. S., GRIFFITH, J. D., GORODETZKY, C. W. and CONE, E. J. Progress report on studies from the Clinical Pharmacology Section of the Addiction Research Center. Presented to Committee on Problems of Drug Dependence, National Research Council--National Academy of Sciences, 1976.

8. JONES, B. E. and PRADA, J. A. Effects of morphine, chlorpromazine and chlordiazepoxide on shock-induced changes in basal skin conductance. *Archives Internationales de Pharmacodynamie et de Therapie* 223: 265-270 (1976).

Chlorpromazine (12.5 and 25 mg/70 kg, i.m.) and chlordiazepoxide (25 and 50 mg/70 kg, i.m.) were compared with morphine (15 and 30 mg/70 kg, i.m.) and placebo in their effects on electric shock-induced increases in basal skin conductance. Morphine and chlorpromazine attenuated the increase compared with placebo, while chlordiazepoxide did not. None of the treatments produced reliable effects on the phasic responses to the stimuli.

9. JONES, B. E., PRADA, J. A. and MARTIN, W. R. A method for bioassay of physical dependence on sedative drugs in dog. *Psychopharmacology* 47: 7-15 (1976).

A method for an economical bioassay of physical dependence on sedatives is presented. Dogs maintained on sodium pentobarbital (200 mg/kg/24 h i.v.) were given periodic graded reductions in maintenance dose, and subscales for measuring signs of abstinence were developed. Using these subscales the relative

ERRATUM: The title of #10 is: Human pharmacology of sleep.

compared with sodium pentobarbital were determined for sodium seco-
RP = 0.85) and methaqualone (RP = 0.14). Sodium thiopental and
ne were assayed and found to be equipotent (RP = 0.96) in reducing
of abstinence from sodium pentobarbital. The occurrence of convul-
ing periods of complete reduction of the maintenance drug, became
ent the longer the dogs had been maintained on a constant dose of
tobarbital.

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R. L. and Karacan, I. (eds.): *Pharmacology of sleep.* pp. 83-210.
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R. Naloxone. *Annals of Internal Medicine* 85: 765-768 (1976).

tic analgesics and related drugs act as agonists on several recep-
are responsible for their effects on pain perception, mood and
ate, and respiration, as well as other pharmacologic actions.
s the first discovered agonist that is devoid of agonistic
nd appears to be a competitive antagonist at several receptors.
y of naloxone to displace or prevent the binding of agonistic
is partly responsible for its antagonistic effects. The ability
e to rectify narcotic-depressed homeostats and precipitate absti-
lso related to its antagonistic activity. Certain cautions and
apply in the use of naloxone in treating narcotic overdose,
surgical analgesia, and the treatment of neonates and children.
uses of naloxone include reversing the psychotomimetic effects of
onists-antagonists, terminating narcotic-induced convulsions and
sing non-narcotic depression, diagnosing physical dependence, and
arcotic addicts.

, BELL, J., GILBERT, P., SLOAN, J. and THOMPSON, J. The effects of
in the chronic spinal dog and acute spinal cat; possible interaction
ally-occurring morphine-like agonists. In: Julius, D. and Renault,
Narcotic antagonists: Naltrexone progress report. pp. 27-30.
aph Series 9, DHEW Publ. 76-387, Rockville, Md. 1976.

R., EADES, C. G., THOMPSON, J. A., HUPPLER, R. E. and GILBERT,
effects of morphine- and nalorphine-like drugs in the nondependent
ne-dependent chronic spinal dog. *Journal of Pharmacology and*
l Therapeutics 197: 517-532 (1976).

different syndromes produced by congeners of morphine have been
in the nondependent chronic spinal dog. These syndromes have been
to interaction of agonists with three distinguishable receptors
). Morphine is the prototype agonist for the μ receptor, keto-
for the κ receptor and SKF-10,047 for the σ receptor. The
ndrome (μ) in the dog is characterized by miosis, bradycardia,
, a general depression of the nociceptive responses and indiff-
environmental stimuli. Ketocyclazocine (κ) constricts pupils,
he flexor reflex and produces sedation but does not markedly
rate or the skin twitch reflex. SKF-10,047 (σ), in contrast to
d ketocyclazocine, causes mydriasis, tachypnea, tachycardia and
effects of these three drugs can be antagonized by the pure
naltrexone, indicating that they are agonists. Further, chronic
ion of morphine, ketocyclazocine and SKF-10,047 induces tolerance
onistic effects. Morphine suppresses abstinence in morphine-
logs while ketocyclazocine does not. Ketocyclazocine at best
d only a liminal abstinence syndrome in the morphine-dependent
ating that it had little affinity for the morphine receptor.
ocine thus appears to be a selective agonist at the κ receptor.
has been shown that buprenorphine is a partial agonist of the
h both suppressed and precipitated abstinence in the morphine-
log while morphine and propoxyphene are stronger agonists.
and SKF-10,047 produce similar pharmacologic effects suggesting
ivity may involve a dopaminergic mechanism.

14. MARTIN, W. R., GILBERT, P. E., THOMPSON, J. A. and JESSE, C. A. Progress report on the animal assessment program of the Addiction Research Center: Use of the chronic spinal dog for the assessment of the abuse potentiality and utility of narcotic analgesics and narcotic antagonists. Presented to Committee on Problems of Drug Dependence, National Research Council--National Academy of Sciences, 1976.

15. MARTIN, W. R., SLOAN, J. W., VAUPEL, D. B., BELL, J. A. and NOZAKI, M. Tryptamine in the brain and spinal cord: Its role in the LSD response. In: Usdin, E. and Sandler, M. (eds.): *Trace amines and the brain.* pp. 83-102. New York: Marcel Dekker 1976.

16. MARTIN, W. R., THOMPSON, J. A. and NOZAKI, M. Physiologic evidence for descending tryptaminergic pathways in the spinal cord. *Life Sciences* 19: 1383-1386 (1976).

LSD was more effective in facilitating the flexor reflex in the chronic than in the acute spinal dog. On the other hand, *l*-tryptophan produced a significant facilitation of the flexor reflex in the acute spinal dog but not in the chronic spinal dog. These data are consistent with the hypothesis that there are long descending tryptaminergic axons which have the capacity of converting tryptophan to tryptamine and releasing it in the vicinity of post-synaptic facilitatory receptors which degenerate in the chronic spinal dog.

17. McCLANE, T. K. and MARTIN, W. R. Subjective and physiologic effects of morphine, pentobarbital and meprobamate. *Clinical Pharmacology and Therapeutics* 20: 192-198 (1976).

These studies extend previous observations on the effects of pentobarbital on subjective states and postrotational nystagmus in postaddict subjects. Pentobarbital (150 mg) induced a degree of liking and an elevation of the morphine-benzedrine group (MBG) scale score equivalent to 24 mg of morphine. The effects of pentobarbital and meprobamate on postrotational nystagmus were studied using electro-oculography. Both drugs increased the frequency and prolonged the duration of postrotational nystagmus in a dose-related manner. Meprobamate was about 1/15 as potent as pentobarbital in enhancing postrotational nystagmus and producing signs of sedation.

18. RISNER, M. E. and JONES, B. E. Characteristics of unlimited access to self-administered stimulant infusions in dogs. *Biological Psychiatry* 11: 625-634 (1976).

When drug-naive dogs were given unlimited access to response-contingent intravenous infusions of either *d*-amphetamine, phenmetrazine, or methylphenidate, a regular cycle of drug intake interspersed with periods of voluntary abstinence was seen. During the drug self-administration phases there was a marked increase in locomotor behavior and stereotypy along with a decrease in body weight; the rest periods were characterized by minimal activity. These results are similar to those observed when humans engage in high-dose intravenous abuse of psychomotor stimulants.

19. RISNER, M. E. and JONES, B. E. Role of noradrenergic and dopaminergic processes in amphetamine self-administration. *Pharmacology, Biochemistry and Behavior* 5: 477-482 (1976)

Dogs were trained to intravenously self-administer *d*-amphetamine (0.05 mg/kg/infusion) until a stable intake per 4 hr daily session was achieved. When the dogs were given noncontingent infusions of *d*-amphetamine in varying amounts (0% to 100% of the baseline intake) immediately prior to the session, they decreased their self-administration response rate appropriately so that total drug intake remained constant. However, there were no changes in subsequent responding for *d*-amphetamine following pretreatment with either the noradrenergic agonist methoxamine (.05-2.0 mg/kg) or the noradrenergic antagonist phenoxybenzamine (1-8 mg/kg). Additionally, responding was not maintained when methoxamine (0.05 mg/kg/infusion) was substituted for

d-amphetamine. In contrast, pretreatment with either the dopaminergic antagonist pimozide (5-40 μg/kg) or chlorpromazine (0.25-2.0 mg/kg) produced dose-dependent increases in the number of self-administered *d*-amphetamine infusions. These data suggest that noradrenergic neurotransmission is not responsible for *d*-amphetamine self-administration, but an intact dopaminergic system does appear to be important.

20. VAUPEL, D. B. and MARTIN, W. R. Actions of methoxamine and tryptamine and their interactions with cyproheptadine and phenoxybenzamine on cat spinal cord segmental reflexes. *Journal of Pharmacology and Experimental Therapeutics* 196: 87-96 (1976).

The effects of norepinephrine, methoxamine and tryptamine were assessed on the monosynaptic and polysynaptic segmental reflexes in the unanesthetized, decerebrated acute spinal cat. Their selectivity of action was determined by studying the interactions of methoxamine and tryptamine with two antagonists, cyproheptadine and phenoxybenzamine. Potentials were evoked by stimulating either the L_7 or S_1 dorsal root and were recorded from the corresponding ipsilateral ventral root. Norepinephrine did not affect reflex activity, whereas methoxamine facilitated both the monosynaptic and polysynaptic potentials in a dose-related manner when infused over 20 minutes. Tryptamine facilitated both the monosynaptic and polysynaptic reflex potentials. This increase was dose related for the monosynaptic reflex but not for the polysynaptic reflex. Phenoxybenzamine blocked the facilitatory effects of methoxamine and did not antagonize the effects of tryptamine on the segmental reflex. The facilitatory effects of tryptamine were effectively blocked by cyproheptadine. Cyproheptadine failed to reduce the polysynaptic response to methoxamine, although it partially antagonized the monosynaptic facilitation. These findings demonstrate that methoxamine and tryptamine facilitate the segmental reflex by different modes of action and provide additional evidence for noradrenergic and tryptaminergic systems in the spinal cord.

21. YEH, S. Y., GORODETZKY, C. W. and McQUINN, R. L. Urinary excretion of heroin and its metabolites in man. *Journal of Pharmacology and Experimental Therapeutics* 196: 249-256 (1976).

The purpose of this study was to investigate the kinetics of urinary excretion of heroin and its metabolites in human subjects. Heroin and its metabolites were determined with gas-liquid chromatography. Two studies were conducted, each using 10 subjects. After i.v. administration of heroin HCl, 10 mg/70 kg, urine was collected every 8 hours and *ad libitum* for 1 week in the first study and every 2 hours in the first 8 hours and then at less frequent intervals for 24 hours in the second study. Heroin, 6-acetylmorphine, morphine, the sum of conjugates (morphine plus 6-acetylmorphine) and total normorphine were determined in the first 24-hour urine and accounted for .05, 1.5, 7.2, 52 and 4%, respectively, of the administered dose. Conjugated morphine could be detected in the urine 96 hours after drug administration. Eighty-eight percent of the free morphine and 84% of the total morphine found in the urine were excreted in the first 8 hours. The half-lives of urinary excretion of free morphine, 6-acetylmorphine, the sum of conjugates (morphine plus 6-acetylmorphine) and total normorphine were 1.28, 1.31, 2.76 and 2.72 hours, respectively. It was concluded that heroin in the body was rapidly metabolized and its metabolites were rapidly excreted in the urine.

AUTHOR INDEX

ANNOTATED BIBLIOGRAPHY

NIDA ADDICTION RESEARCH CENTER
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1977

1. BELL, J. A. and MARTIN, W. R. The absence of an effect of L-trytophan on the C-fiber reflex in the chronic spinal cat. *Life Sciences* 20: 1087-1090 (1977).

   L-tryptophan (150 mg/kg) had no effect on the C-fiber reflex in the acute decerebrate chronic spinal cat. L-tryptophan had been previously shown to facilitate this reflex in the acute decerebrate acute spinal cat. This finding supports the hypothesis that tryptaminergic neurons in the brain have axons which descend the spinal cord to produce modulation of some spinal reflexes.

2. BELL, J. A. and MARTIN, W. R. The effect of the narcotic antagonists naloxone, naltrexone and nalorphine on spinal cord C-fiber reflexes evoked by electrical stimulation or radiant heat. *European Journal of Pharmacology* 42: 147-154 (1977).

   C-fiber reflexes were recorded from an S_1 ventral root in the acute decerebrate low spinal cat following stimulation of the ipsilateral superficial peroneal nerve or application of radiant heat to the metacarpel footpad. Naloxone when administered i.v. increased the electrically evoked C-fiber reflex to 158% (± 23.8% S.E.M.) of control 10 min after administration; whereas, naltrexone, 0.0025 mg/kg, increased the C-fiber reflex to 206 ± 26.1% (S.E.M.) of control. Naloxone in a dose of 0.050 mg/kg increased the radiant heat evoked ventral root reflex to 161 ± 19.5% of control. Nalorphine, 1 mg/kg, facilitated the electrically evoked C-fiber reflex to 282 ± 75% of control. These findings that naloxone and naltrexone facilitated these reflexes in doses too small to have nonspecific excitatory effects and that nalorphine facilitated the C-fiber reflex at a dose level that is depressant to the flexor reflex in the chronic spinal dog are consistent with a hypothesis that these effects are due to antagonism of a naturally-occurring opiate-like inhibitory substance.

3. CONE, E. J., PHELPS, B. A. and GORODETZKY, C. W. Urinary excretion of hydromorphone and metabolites in humans, rats, dogs, guinea pigs, and rabbits. *Journal of Pharmaceutical Sciences* 68: 1709-1713 (1977).

   Hydromorphone was administered as a single dose to humans, rats, dogs, guinea pigs, and rabbits, and timed urinary collections were made. GLC-mass spectrometric and GLC analyses of the samples revealed the presence of the parent compound and both 6-hydroxy epimers as metabolites in the urine of all species. Free or conjugated parent drug predominated, while levels of free or conjugated 6β-hydroxy metabolite were higher than or equal to those of the 6α-form. The time courses of excretion of drug and metabolites were similar for all species, with the major portion being excreted in the first 24 hr. Generally, free and conjugated drug were undetectable in human urine after 8 and 48 hr, respectively.

4. FRASER, H. F. and JASINSKI, D. R.: The assessment of the abuse potentiality of sedative/hypnotics (depressants) (Methods used in animals and man). In: Martin, W. R. (ed.): *Drug addiction I: Morphine, sedative/hypnotic and alcohol dependence*. Handbook of Experimental Pharmacology, Vol. 45. pp. 589-612. Heidelberg: Springer-Verlag 1977.

5. GILBERT, P. E. and MARTIN, W. R. Antagonism of the effects of pentobarbital in the chronic spinal dog by naltrexone. *Life Sciences* 20: 1401-1406 (1977).

Some of the actions of pentobarbital in the chronic spinal dog were antagonized by naltrexone. Pentobarbital depressed the flexor reflex and the level of consciousness, and these actions of pentobarbital were partially antagonized by naltrexone. Naltrexone alone did not alter these functions. Pentobarbital also increased the latency of the skin twitch reflex, decreased pupillary diameter and depressed pulse and respiratory rates. The data are consistent with the hypothesis that some of the actions of pentobarbital may be mediated through functional systems involving the κ receptor.

6. GILBERT, P. W., MARTIN, W. R. and JESSEE, C. A. Use of the chronic spinal dog for the assessment of the abuse potentiality and utility of narcotic analgesics and narcotic antagonists. Presented to Committee on Problems of Drug Dependence, National Research Council--National Academy of Sciences, 1977.

7. GORODETZKY, C. W. Detection of drugs of abuse in biological fluids. In: Martin, W. R. (ed.): *Drug addiction I: Morphine, sedative/hypnotic and alcohol dependence.* Handbook of Experimental Pharmacology, Vol. 45. pp. 319-409. Heidelberg: Springer-Verlag 1977.

8. GRIFFITH, J. D. Amphetamine dependence; clinical features. In: Martin, W. R. (ed.): *Drug addiction II: Amphetamine, psychotogen, and marihuana dependence.* Handbook of Experimental Pharmacology, Vol. 45. pp. 277-304. Heidelberg: Springer-Verlag 1977.

9. JASINSKI, D. R. Assessment of the abuse potentiality of morphinelike drugs (methods used in man). In: Martin, W. R. (ed.): *Drug addiction I: Morphine, sedative/hypnotic and alcohol dependence.* Handbook of Experimental Pharmacology, Vol. 45. pp. 197-258. Heidelberg: Springer-Verlag 1977.

10. JASINSKI, D. R. Clinical evaluation of sedative-hypnotics for abuse potential. In: Thompson, T. and Unna, K. (eds.): *Predicting dependence liability of stimulant and depressant drugs.* pp. 285-289. Baltimore: University Park Press 1977.

11. JASINSKI, D. R., GRIFFITH, J. D., PEVNICK, J., GORODETZKY, C., CONE, E. and KAY, D. Progress report from the Clinical Pharmacology Section of the NIDA Addiction Research Center. Presented to Committee on Problems of Drug Dependence, National Research Council--National Academy of Sciences, 1977.

12. JASINSKI, D. R., NUTT, J. G., HAERTZEN, C. A., GRIFFITH, J. D. and BUNNEY, W. E. Lithium: Effects on subjective functioning and morphine-induced euphoria. *Science* 195: 582-584 (1977).

The therapeutic usefulness of lithium in decreasing the euphoria and other symptoms associated with manic behavior and the hypothesis of a common final mechanism for elevations in mood have led to speculation that lithium may block the euphoria induced by drugs of abuse. In this study, lithium alone was antieuphoric in drug-free opiate addicts and, further, did not block morphine-induced euphoria.

13. JASINSKI, D. R., PEVNICK, J. S., CLARK, S. C. and GRIFFITH, J. D. Therapeutic usefulness of propoxyphene napsylate in narcotic addiction. *Archives of General Psychiatry* 34: 227-233 (1977).

The maximum doses of propoxyphene napsylate used to treat heroin addicts produce a degree of morphine-like activity equal to that produced by 20 to 25 mg/day of subcutaneously given morphine or 10 mg/day orally given methadone. This degree of activity would be sufficient to ameliorate abstinence even in patients dependent on large doses of narcotics--an observation that supports the utility of propoxyphene napsylate in detoxification. On the other hand, only patients taking 10 mg/day or less of parenterally administered heroin could be maintained on maximum subtoxic levels of propoxyphene napsylate without abstinence signs or symptoms suggesting that propoxyphene napsylate would be less useful in maintenance therapy.

14. JONES, B. E. Predicting abuse liability of depressant drugs. In: Thompson, T. and Unna, K. (eds.): *Predicting dependence liability of stimulant and depressant drugs*. pp. 35-46. Baltimore: University Park Press 1977.

15. JONES, B. E. and PRADA, J. A. Drug-seeking behavior in the dog: Lack of effect of prior passive dependence on morphine. *Drug and Alcohol Dependence* 2: 287-294 (1977).

Twelve dogs were made dependent on morphine (20 mg/kg per 24 hours) by intravenous passive administration of the drug. Six were gradually withdrawn and six were withdrawn abruptly. Subsequent tests for self-administration of morphine began within 8 to 18 weeks after morphine was last administered passively. Morphine was available for self-administration at several unit dose levels for 8 weeks. In comparison with control dogs administered with saline, there was no evidence that prior dependence on morphine influences subsequent self-administration of morphine, or that morphine is a primary reinforcer for dogs. Possible implications of these and related observations are discussed.

16. JONES, B. E. and PRADA, J. A. Effects of methadone and morphine maintenance on drug-seeking behavior in dog. Presented to Committee on Problems of Drug Dependence, National Research Council--National Academy of Sciences,1977.

17. JONES, B. E. and PRADA, J. A. Effects of methadone and morphine maintenance on drug-seeking behavior in the dog. *Psychopharmacology* 54: 109-112 (1977).

The effects of methadone and morphine maintenance on morphine self-administration were studied in the dog. Methadone was given passively for 2 weeks by continuous i.v. infusion. The amount of methadone administered daily was the same in mg/kg as the mean daily mg/kg of morphine the dogs had self-administered during the premaintenance control week. Morphine self-administration was markedly reduced initially but returned to normal levels within 2 weeks of methadone administration. Following the methadone maintenance period, morphine self-administration was increased over the premaintenance period for 2 weeks. A result similar to that with methadone was obtained in a second experiment when morphine was used as the maintenance drug in an amount that was three times the amount the dogs had been self-administering during the premaintenance control week.

18. KRIVOY, W., KROEGER, D. and ZIMMERMANN, E. Additional evidence for a role of substance P in modulation of synaptic transmission. In: von Euler, U. S. and Pernow, B. (eds.): *Substance P*. pp. 187-193. New York: Raven Press 1977.

Using α-motoneurones as a model for studying actions of SP on synaptic transmission it was found that SP facilitates post-detonation recovery of excitability. This is in accord with the hypothesis that SP modulates neural activity, and that this is its physiological role. It may also explain the mechanism by which SP antagonizes morphine.

19. KRIVOY, W. A., KROEGER, D. C. and ZIMMERMANN, E. Neuropeptides: Influence of acute and chronic effects of opiates. *Psychoneuroendocrinology* 21: 43-51 (1977).

(1) There is a variety of naturally occurring polypeptides that influence the actions of morphine. (2) Some of these may be physiological modulators, altering synaptic excitability in a direction that is the same as or opposite to the changes in modulation produced by morphine, so as to mimic or antagonize the actions of morphine. (3) Other polypeptides appear to act via different mechanisms so as to mimic or antagonize the actions of morphine, or to influence the body's response to morphine. (4) Finally, it is fully appropriate to evaluate critically the important work on what has become known as "the morphine receptor" and consider it from the more conservative reference point of "a morphine receptor".

20. KRIVOY, W. A., STEWART, J. M. and ZIMMERMANN, E. Analgesic actions of substance P. In: von Euler, U. S. and Pernow, B. (eds.): *Substance P.* pp. 195-200. New York: Raven Press 1977.

The hotplate technique was used to test for the influence of SP and of MS on pain. It was found that when given intracerebrally, both SP as well as MS produced analgesia that was antagonized by naloxone. Cross-tolerance to SP was observed in mice given chronic morphine.

21. KRIVOY, W. A. and ZIMMERMANN, E. An effect of β-melanocyte stimulating hormone (β-MSH) on α-motoneurones of cat spinal cord. *European Journal of Pharmacology* 46: 315-322 (1977).

Actions of β-MSH and of melatonin on the recovery cycle of single spinal neurones were studied in the decerebrate-spinal cat. β-MSH facilitated the rate of post-excitation recovery of α-motoneurones and some internuncial neurones, and melatonin inhibited the rate of post-excitation recovery. These observations provide additional evidence that β-MSH functions in the nervous system as a modulator, and may help explain actions of β-MSH in modifying acquisition of conditioned avoidance responses as well as its interaction with drugs such as morphine.

22. MARTIN, W. R. Assessment of depressant abuse potentiality. In: Thompson, T. and Unna, K. (eds.): *Predicting dependence liability of stimulant and depressant drugs.* pp. 9-15. Baltimore: University Park Press 1977.

23. MARTIN, W. R. Chemotherapy of narcotic addiction. In: Martin, W. R. (ed.): *Drug addiction I: Morphine, sedative/hypnotics and alcohol dependence.* Handbook of Experimental Pharmacology, Vol. 45. pp. 279-318. Heidelberg: Springer-Verlag 1977.

24. MARTIN, W. R. Dependence on narcotic analgesics. In: Pradhan, S. N. (ed.) and Dutta, S. N. (assoc. ed.): *Drug abuse: Clinical and basic aspects.* pp. 201-210. St. Louis: C. V. Mosby 1977.

25. MARTIN, W. R. Drugs and drug addiction. Presented to Committee on Problems of Drug Dependence, National Research Council--National Academy of Sciences, 1977.

26. MARTIN, W. R. General problems of drug abuse and drug dependence. In: Martin, W. R. (ed.): *Drug addiction I: Morphine, sedative/hypnotic and alcohol dependence.* Handbook of Experimental Pharmacology, Vol. 45. pp. 3-40. Heidelberg: Springer-Verlag 1977.

27. MARTIN, W. R., HEWETT, B. B., BAKER, A. J. and HAERTZEN, C. A. Aspects of the psychopathology and pathophysiology of addiction. *Drug and Alcohol Dependence* 2: 185-202 (1977).

It is proposed that one of the important dimensions of drug addiction is the presence of increased need states which give rise to impulsivity, egocentricity and feelings of hypophoria. To attempt to obtain additional information bearing on this hypothesis, a Maturation Scale was designed which has items related to feelings of impulsivity, egocentricity, needs, hypophoria and sociopathy. The Minnesota Multiphasic Personality Inventory (MMPI) and Maturation Scale were administered to 54 control subjects who were students or faculty members at a religious college and seminary, 53 alcoholics, and 24 prisoner drug abusers. In addition, blood levels of follicle stimulating hormone (FSH), luteinizing hormone (LH) and testosterone were determined. It was found that scores on the Maturation Scale and the Impulsivity, Egocentricity, Need and Sociopathy Subscales of the Maturation Scale were significantly elevated in alcoholic and prisoner subjects. Alcoholics and prisoners also had significantly elevated Psychopathic Deviate (Pd), Hypomania (Ma) and Depression (D) Scale scores and plasma levels of LH and testosterone but not FSH. The fact that the Maturation Scale and its subscales and other psychologic measures related to the antisocial personality tended to covary for alcoholics and prisoners, and that these two criterion groups had elevated

LH and testosterone levels, supports the need concept of drug addiction. The Maturation Scale, which measures immaturity and tests existing feeling states, appears to be a discriminative and useful tool for assessing the status of the psychopathology of drug abusers.

28. MARTIN, W. R. and JASINSKI, D. R. Assessment of the abuse potential of narcotic analgesics in animals. In: Martin, W. R. (ed.): *Drug addiction I: Morphine, sedative/hypnotic and alcohol dependence.* Handbook of Experimental Pharmacology, Vol. 45. pp. 159-196. Heidelberg: Springer-Verlag 1977.

29. MARTIN, W. R. and KAY, D. C. Effects of opioid analgesics and antagonists on the EEG. In: Longo, V. G. (ed.): *Handbook of electroencephalography and clinical neurophysiology,* Vol. 7, Part C. pp. 97-109 (references pp. 110-131). Amsterdam: Elsevier 1977.

The effects of opioid analgesics and opioid antagonists on sensation, perception, mood, consciousness and thought process are complex, and in some instances, paradoxical. The complexity of their actions may be related to their multiple mechanisms of action. Neuropharmacologic studies have been of particular value in analyzing the site and mode of action of these drugs regarding four phenomena: analgesia, sedation or narcosis, mood changes such as euphoria, and seizure activity. It will be the purpose of this Section to review the literature on the effects of opioids and opioid antagonists on spontaneous and evoked cortical activity and where possible to place these observations in meaningful conceptual frameworks.

30. MARTIN, W. R. and SLOAN, J. W. Neuropharmacology and neurochemistry of subjective effects, analgesia, tolerance, and dependence produced by narcotic analgesics. In: Martin, W. R. (ed.): *Drug addiction I: Morphine, sedative/hypnotic and alcohol dependence.* Handbook of Experimental Pharmacology, Vol. 45. pp. 43-158. Heidelberg: Springer-Verlag 1977.

31. MARTIN, W. R. and SLOAN, J. W. Pharmacology and classification of LSD-like hallucinogens. In: Martin, W. R. (ed.): *Drug addiction II. Amphetamine, psychotogen and marihuana dependence.* Handbook of Experimental Pharmacology, Vol. 45. pp. 305-368. Heidelberg: Springer-Verlag 1977.

32. MARTIN, W. R., VAUPEL, D. B., NOZAKI, M. and BRIGHT, L. D. The identification of LSD-like hallucinogens using the chronic spinal dog. Presented to Committee on Problems of Drug Dependence, National Research Council--National Academy of Sciences, 1977.

33. NOZAKI, M., BELL, J. A., VAUPEL, D. B. and MARTIN, W. R. Responses of the flexor reflex to LSD, tryptamine, 5-hydroxytryptophan, methoxamine, and d-amphetamine in acute and chronic spinal rats. *Psychopharmacology* 55: 13-18 (1977).

The flexor reflex of acute (40-48 h after mid-thoracic spinal transection) and chronic (at least 2 months after transection) spinal rats was evoked by tetanic electrical stimulation of both hindfeet and recorded on a polygraph using a transducer connected to the left hindfoot. The flexor reflex in the chronic spinal rat was more responsive to electrical stimulation and to the actions of drugs studied than was the flexor reflex in the acute spinal rat. In chronic spinal rats, *d*-amphetamine, methoxamine, LSD, tryptamine, and 5-hydroxytryptophan (5-HTP) facilitated the flexor reflex and induced spontaneous movements. These facilitative effects were seen in acute spinal rats only when much larger i.p. doses of amphetamine, methoxamine, and LSD were used. Small i.v. doses of tryptamine also produced the facilitation. The facilitation caused by LSD and tryptamine, but not 5-HTP, in chronic spinal rats was antagonized by cyproheptadine. These observations suggest that chronic spinal rats were more sensitive to the drugs than acute spinal rats and support the hypothesis that the mode of action of LSD is similar to that of tryptamine but different from that of 5-HTP since cyproheptadine antagonized the facilitative effects of LSD and tryptamine but not those of 5-HTP.

34. NOZAKI, M., VAUPEL, D. B. and MARTIN, W. R. A pharmacologic comparison of 3,4-methylenedioxyamphetamine and LSD in the chronic spinal dog. *European Journal of Pharmacology* 46: 333-349 (1977).

MDA (2.0 and 2.2 mg/kg) was compared to LSD (10 μg/kg)and *d*-a (3.2 mg/kg) in single dose, antagonism, cross tolerance and appet sion studies. In single doses MDA specifically resembled *d*-amphe producing marked mydriasis, nictitating membrane retraction, ster darting eye movements and LSD by markedly facilitating the flexor producing continuous stepping, whining and eye tracking movements. MDA increased respiration, body temperature and the latency of the twitch reflex and produced behavioral arousal. Cyproheptadine an the effects of LSD but was ineffective against MDA. Phenoxybenzam nized the respiratory, pupillary and hyperthermic effects of MDA a respiratory effect of LSD. Chlorpromazine antagonized many of the LSD and MDA. Spinal dogs were made tolerant to the behavioral and effects of LSD. Cross tolerance developed to some but not all of of MDA. In intact dogs MDA was 1/10 as potent as *d*-amphetamine in appetite. It is concluded that MDA has properties resembling both amphetamine.

35. PICKWORTH, W. B., SHARPE, L. G. and MARTIN, W. R. Transcallosally potentials and the EEG in the decerebrate dog: Actions of tryptami dopaminergic and adrenergic agonists. *Electroencephalography and Neurophysiology* 42: 809-816 (1977).

The midpontine decerebrate dog, immobilized with gallamine, w determine the changes in the transcallosally evoked potential (TEP by intravenous infusions of various drugs. A total of 50 TEPs, re the g. ectolateralis, was computer analyzed before, during and aft tration of the drugs. Changes in the TEP were also correlated wit the EEG recorded from the g. ectolateralis. The EEG was analyzed and amplitude integration (electrogenesis). LSD (30 μg/kg) signif depressed the TEP, and the effect persisted for at least 80 min. caused a significant and reversible increase in the amplitude of t and DMT reduced the alpha activity of the EEG and enhanced the ampl the low-frequency waves. DMT produced a significant and LSD a marg in electrogenesis. Tryptamine (10 and 20 mg/kg), mescaline (6 mg/k amine (0.88 mg/kg) and apomorphine had no significant effect on the These results suggest that depression of the TEP is not related to reflex facilitation in the dog or hallucinogenic activity in man.

36. PICKWORTH, W. B., SHARPE, L. G., NOZAKI, M. and MARTIN, W. R. *Expe Neurology* 57: 999-1011 (1977).

Central adrenergic mechanisms have been implicated in behavior We studied the effects of methoxamine, a long-acting direct α-adren agonist. Cortical and hippocampal electroencephalograms, nuchal el myograms, and electrooculograms were recorded from beagle-type dogs isolation chamber while their behavior was observed on a videomonit Following intravenous saline, total sleep occurred during 61 ± 6.0% 2-h recording period. Of that time, 35 ± 4.5% was in light sleep, was in slow-wave sleep, and 11 ± 1.2% was in paradoxical sleep. An dose of 0.33 mg/kg methoxamine caused no significant changes, where kg dose significantly reduced total sleep (25 ± 5.7%) and paradoxica (3 ± 1.2%). When infused into the dorsal aspect of the third ventri methoxamine (100, 400 or 1200 μg) produced no significant effects. these doses of methoxamine injected into the ventral third ventricle a significant dose-related increase in total sleep, slow-wave sleep, paradoxical sleep and an increase in light sleep. Phenoxybenzamine intravenously) pretreatment significantly antagonized the arousal ef methoxamine (400 μg) administered into the ventral third ventricle. tribution of infusions of a contrast medium and bromphenol blue into dorsal and ventral third ventricle differed in that infusions at the site did not reach anterior hypothalamic structures. In other exper tritium-labeled methoxamine was found to cross the blood-brain barri rat. These results suggest that methoxamine is a centrally active α agonist and support the concept that hypothalamic adrenergic mechani involved in electroencephalographic and behavioral arousal.

ERRATUM: The title of #36 is: Sleep suppression induced by intravenous and intraventricular infusions of methoxamine in the dog.

37. RISNER, M. E. and JONES, B. E. Characteristics of β-phenethylamine self-administration by dog. *Pharmacology, Biochemistry and Behavior* 6: 689-696 (1977).

Phenethylamine (PEA), a biologically active amine found in the brain, maintained intravenous self-administration behavior by dogs previously trained to respond for amphetamine. Systematic changes in the unit dose of PEA (1.5 to 6.0 mg/kg/infusion) were negatively related to the number of infusions (91.3 to 29.5, respectively) per 4 hr session. The mean intake of PEA was 165 mg/kg/session. Pretreatment with chlorpromazine (0.5 to 2.0 mg/kg, IV, 30 min prior to the session) produced a dose-dependent increase in the number of self-administered PEA infusions. However, there were no changes in responding for PEA following pretreatment with either the dopaminergic antagonist pimozide (5 to 40 μg/kg, IV, 30 min prior to the session) or the adrenergic antagonist phenoxybenzamine (1 to 8 mg/kg, IV, 30 min prior to the session). These data suggest that the reinforcing properties of PEA are not dependent on either a dopaminergic or adrenergic system.

38. SHARPE, L. G., PICKWORTH, W. B. and MARTIN, W. R. Actions of amphetamine and antagonists on pupil diameter in the chronic sympathectomized dog. *Psychopharmacology* 53: 115-120 (1977).

The left superior cervical ganglia were removed from 5 dogs. Beginning 30 days postoperatively, epinephrine (10 μg/kg/min), norepinephrine (10 μg/kg/min), and *d*-amphetamine (10 mg/kg) were infused i.v. for 10 min following either vehicle, phenoxybenzamine, pimozide, or haloperidol. Epinephrine and norepinephrine dilated the pupil and retracted the nictitating membrane of the denervated side, whereas amphetamine dilated both pupils and retracted both nictitating membranes. Phenoxybenzamine (4 mg/kg) constricted primarily the pupil of the innervated iris and completely antagonized the effects of the catecholamines on the irides and amphetamine on the nictitating membranes, but only partially antagonized amphetamine-induced mydriasis. Haloperidol (1.0 mg/kg) constricted both pupils, possessed only modest α-adrenergic blocking activity, and was as effective as phenoxybenzamine in antagonizing amphetamine-induced mydriasis. Pimozide (0.1 mg/kg) constricted both pupils, had no significant α-adrenergic blocking activity, and did not antagonize amphetamine-mydriasis. Pimozide and haloperidol, but not phenoxybenzamine, blocked the amphetamine-induced stereotyped head bobbing. These results suggest that amphetamine produces mydriasis in the dog through a peripheral sympathetic action and also through a central mechanism involving inhibition of the oculomotornucleus. However, the role of dopamine is not clear.

39. VAUPEL, D. B., MARTIN, W. R., BRIGHT, L. D. and NOZAKI, M. Single dose and cross tolerance studies of LSD, *d*-amphetamine, β-phenethylamine and 4-bromo-2,5-dimethoxyamphetamine in the chronic spinal dog. Presented to Committee on Problems of Drug Dependence, National Research Council--National Academy of Sciences, 1977.

40. VAUPEL, D. B., NOZAKI, M. and MARTIN, W. R. A pharmacologic comparison of 2,5-dimethoxyamphetamine and LSD in the chronic spinal dog. *Drug and Alcohol Dependence* 2: 45-63 (1977).

Intravenous infusions of 2,5-dimethoxyamphetamine (2.4 mg/kg) and LSD (10 μg/kg) in the chronic spinal dog facilitated the flexor reflex, elicited the stepping reflex, increased respiration, produced a modest pupillary dilation and raised body temperature and were approximately equieffective. Cyproheptadine (0.2 mg/kg) alone antagonized the effects of LSD and 2,5-dimethoxyamphetamine (DMA) on the stepping reflex, and both cyproheptadine and phenoxybenzamine (1.0 mg/kg) reduced the actions of LSD and DMA on respiration and pupillary diameter. In another group of chronic spinal dogs tolerant to 30 μg/kg/day of LSD, cross tolerance was present to the effects of DMA on the flexor and stepping reflexes, respiration, mydriasis, temperature and behavior. Additional evidence suggested that direct tolerance to DMA can be produced and that these animals are cross tolerant to LSD. In intact dogs DMA exerted an anorexigenic effect, but was less potent than

d-amphetamine. Generally the LSD-like actions of DMA were more pronounced than its amphetamine-like qualities and some actions are indicative of a mixture of drug effects.

41. YEH, S. Y., GORODETZKY, C. W. and KREBS, H. A. Isolation and identification of morphine 3- and 6-glucuronides, morphine 3,6-diglucuronide, morphine 3-ethereal sulfate, normorphine, and normorphine 6-glucuronide as morphine metabolites in humans. *Journal of Pharmaceutical Sciences* 66: 1288-1293 (1977).

Morphine metabolites were isolated with column chromatography on a resin and neutral aluminum oxide and TLC from the urine of morphine-dependent subjects maintained on morphine sulfate at a dose of 240 mg/day. These metabolites were characterized as morphine 3-glucuronide, morphine 6-glucuronide, morphine 3,6-diglucuronide, morphine 3-ethereal sulfate, normorphine, normorphine 6-glucuronide, and possibly, normorphine 3-glucuronide by free phenol and glucuronide tests, enzymatic hydrolysis, GLC, TLC, UV spectroscopy, and GLC-mass spectrometry.

42. YEH, S. Y., McQUINN, R. L. and GORODETZKY, C. W. Biotransformation of morphine to dihydromorphinone and normorphine in the mouse, rat, rabbit, guinea pig, cat, dog, and monkey. *Drug Metabolism and Disposition* 5: 335-342 (1977).

Biotransformation of morphine to dihydromorphinone and normorphine was studied in several mammalian species. Free and total dihydromorphinone, morphine, and normorphine in the urine were determined, as propionyl derivatives, with a gas-chromatographic technique. Dihydromorphinone was detected as a morphine metabolite in the acid-hydrolyzed urine of all species studied except the dog and morphine-dependent man. Normorphine in both free and conjugated forms was detected in the urine of all species studied. The degree of biotransformation of morphine to dihydromorphinone in the guinea pig did not change during chronic administration of morphine sulfate, 25 mg/kg, daily for 28 days. The small amounts of dihydromorphinone and normorphine produced as metabolites make it unlikely that they play any significant role in the modification of the pharmacologic effects of morphine.

43. YEH, S. Y., McQUINN, R. L. and GORODETZKY, C. W. Identification of diacetylmorphine metabolites in humans. *Journal of Pharmaceutical Sciences* 66: 201-204 (1977).

With the techniques of column chromatography, TLC, and GLC, morphine, 6-acetylmorphine, normorphine, morphine 3-glucuronide, 6-acetylmorphine 3-glucuronide, and normorphine glucuronide were identified as metabolites of diacetylmorphine (heroin) in the urine of humans administered 10 mg iv/70 kg body weight.

AUTHOR INDEX

ANNOTATED BIBLIOGRAPHY OF PAPERS FROM THE ADDICTION RESEARCH CENTER

1935–75

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
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National Institute on Drug Abuse
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FOREWORD

The Addiction Research Center, the intramural research program for the National Institute on Drug Abuse, began the first studies of the narcotic addiction process under controlled circumstances in the U.S. Prison Annex at Leavenworth, Kansas, in 1933. A few years later, this pioneer program was moved to the Narcotic Farm at Lexington, Kentucky. It was renamed the Addiction Research Center (ARC) when it was transferred to the newly created National Institute of Mental Health in 1948. Until the middle 1960's, a relatively small cadre of investigators at the Addiction Research Center conducted a large portion of the world's basic and clinical investigations into narcotic addiction. ARC also produced many of the leaders of the National Institute of Mental Health.

The clinical utility of the observations made by scientists at ARC has only recently become recognized. It is hoped that this new bibliography will be helpful to biomedical investigators and other drug abuse professionals in rediscovering some of this now classic research and, in this way, facilitating the continuing search for new and useful ways of dealing with the important medical and social problems of drug abuse.

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Director
National Institute on Drug Abuse

PREFACE

In May of 1975 a symposium was held at the Addiction Research Center on the occasion of its 40th anniversary in which the history of the Federal Government's involvement in problems of drug abuse, particularly that part that was related to the Lexington and Fort Worth facilities and the Addiction Research Center, was recounted. The papers presented are published in a companion volume (1). At the time of this symposium Dr. Robert C. Petersen was in the process of compiling the titles and abstracts of papers emanating from extramural projects funded by the Division of Research of the National Institute on Drug Abuse and suggested that a similar compilation of the papers of the Addiction Research Center might be useful.

There were several reasons why this suggestion was appealing. The Addiction Research Center has been the major intramural program of the National Institute of Mental Health and the National Institute on Drug Abuse concerned with the problem of narcotic addiction, and it was felt that the published bibliography would serve as a public record of the accomplishments of this endeavor. The Addiction Research Center has been a unique laboratory in that a balance between clinical and basic research has been maintained. Further, in fulfilling the Surgeon General's responsibility in advising about the abuse potential of narcotic analgesics, there was also a productive balance between operational and basic research. Finally, the Addiction Research Center was located physically in a large prison hospital and the resulting day-to-day contact with drug abusers provided a circumstance where investigators could derive a realistic and intuitive feeling about the nature of the addiction process.

Beginning in 1967 the character of the hospital began to change and with these changes came marked and continuing changes in the program of the Addiction Research Center which have not yet fully run their course. At the time of this writing, the use of prisoners as research subjects is being phased out and with it the opportunity of studying addictive processes under controlled circumstances. Much of our knowledge of the clinical characteristics of drug abuse has been derived from these experiments and from the participation of prisoner narcotic addicts. The final beneficiaries of these studies, which were responsible for the development of safe and humane ways of detoxification, the identification of the beneficial properties of the treatment modalities methadone, LAAM, cyclazocine, naloxone, and naltrexone, and the prevention of the introduction of new addicting analgesics, were addicts.

It is hoped that this volume and its companion volume[1] will provide a ready and useful reference source for students of the addictive processes.

Barbara Smith, Lula Moore, Wanda Roberts, Barbara Tussey, Linda Rothwell, Phyllis Tackett, and Glenna Kuhnapfel of the staff of the Addiction Research Center compiled and organized the references.

William R. Martin
Director, Addiction Research Center
National Institute on Drug Abuse

[1]W.R. Martin and Harris Isbell (eds.): *Drug Addiction and the United States Public Health Service: Proceedings of Symposium Commemorating the Fortieth Anniversary of the Establishment of the Addiction Research Center at Lexington, Ky.* DHEW Publication No. (ADM) 77–434. National Institute on Drug Abuse. Washington D.C., Superintendent of Documents, U.S. Government Printing Office, 1978.

1935

1. Brown, R.R.: Drug addiction in its relation to extroversion, ambiversion, and intraversion. *Journal of Applied Psychology* 19:555–563 (1935).

McDougall's hypothesis concerning the close affinity between introversion and the alkaloid drugs is not borne out by anthropometric studies reported. The average morphine addict coming within the purview of observation falls into the pyknoid group. The Bernreuter Personality Schedule and the Neymann-Kohlstedt Introversion-Extroversion Schedule are of limited scope in connection with studies on drug addiction.

2. Himmelsbach, C.K., Gerlach, G.H., and Stanton, E.J.: A method for testing addiction, tolerance, and abstinence in the rat. Results of its application to several morphine alkaloids. *The Journal of Pharmacology and Experimental Therapeutics* 53:179–188 (1935).

The irritability of rats, as measured by their struggle responsiveness to a uniformly uncomfortable situation, was determined weekly while they were receiving daily injections of morphine, heroin, or codeine for 5 to 6 weeks, and on alternate days after permanent withdrawal for 9 to 13 days. They were found to show definite and increasing preinjection irritability; incomplete postinjection tranquilization during the addiction period, but almost complete in the case of heroin; and gradual decrease to normal irritability during the first 7 to 10 days of permanent abstinence. Control animals receiving daily injections of water did not show these phenomena. The tendencies exhibited by the animals receiving daily injections of morphine, heroin, or codeine are interpreted as indicating the presence of addiction (abstinence phenomena on withdrawal of the drug) and tolerance. Tolerance in the rat as measured by this method is a summation of at least two actions, both of which tend to reduce the number of postinjection movements: suppression of discomfort and the production of a cataleptic state. Observation indicates that tolerance to the sedative effect may be more easily acquired than tolerance to the cataleptic state. The method, according to control data, does not give false positive results and is completely objective, simple, and relatively inexpensive. The data obtained with its use conform with clinical experience relative to the drugs used.

1936

3. Himmelsbach, C.K.: Chemico-pharmacological studies of morphine and allied drugs. III. Clinical studies. *Hospital News* 3:32–36 (1936).

4. Williams, E.G.: General outline of research on the nature of drug addiction in man. *Hospital News* 3:9–18 (1936).

1937

5. Himmelsbach, C.K.: Clinical studies of drug addiction. I. The absence of addiction liability in "perparin." *Public Health Reports* Supp. 122 (1937).

"Perparin" administered in the manner and amounts described is without demonstrable addiction liability. "Perparin" is without demonstrable value in the treatment of the abstinence syndrome.

6. Himmelsbach, C.K.: Clinical studies of drug addiction. II. "Rossium" treatment of drug addiction. *Public Health Reports* Supp. 125 (1937).

"Rossium" was found to be without demonstrable beneficial effect on the abstinence syndrome, whether administered alone or in combination with certain therapeutic agents. The therapeutic agents that have been recommended for use with "Rossium" (dextrose phleboclysis, barbiturates, and insulin) were found to be without beneficial effect on the abstinence syndrome, except that dextrose phleboclysis usually gave temporary subjective relief.

7. Himmelsbach, C.K.: The nursing care of drug addicts. *The Trained Nurse and Hospital Review* 99:495–497 (1937).

Addicts react to withdrawal by characteristic physical signs and symptoms and an unusual emotional swing. It should be appreciated that addicts vary in the severity of their withdrawal discomfort and their reaction to it; some suffer much and complain little, while others suffer little but complain bitterly. Accurate nurses' observations of the characteristic physical signs of withdrawal are of definite value in the adaptation of treatment to individual cases. Patients undergoing withdrawal require careful nursing with strict attention to the physical and emotional changes which may portend disaster, or indicate a different form of treatment. Certain nursing procedures are of definite value in reducing abstinence discomfort. A method for differentiating between real

abstinence discomfort, impending collapse, and malingering has been presented.

1938

8. Andrews, H.L.: The physical basis of brain potential recording. *Southern Medical Journal* 31:315–320 (1938).

9. Brown, R.R.: Effect of age on the speed-power relationship with reference to tests of intelligence. *Journal of Educational Psychology* 29:413–418 (1938).

Speed and power tests for nonverbal analogies were constructed and applied to a drug addict population containing old, middle, and young age groups. The results indicated a tendency for the young group to exceed the old on the speed test, although both groups were about equal on the power test. When interpreted in light of findings reported in the literature, the results offer further substantiation of a true difference between old and young persons with respect to the speed-power relationship. The need for differentiation of speed from power factors has been discussed with reference to application of intelligence tests to penitentiary and drug addict populations.

10. Brown, R.R. and Vogel, V.H.: Psycho-physiological reactions following painful stimuli under hypnotic analgesia contrasted with gas anaesthesia and novocain block. *Journal of Applied Psychology* 22:408–420 (1938).

Quantitative changes in physiological reactions to painful stimuli are not reliable indicators of painful experience. Nitrous oxide anesthesia abolishes physiological reactions to moderately intense sensory stimuli. (Severe stimuli were not used.) Suggested analgesia in the hypnotic state does not abolish physiological reactions to sensory stimuli. Suggested deafness does not abolish physiological reactions to auditory stimuli. Awareness of stimulation appears to be one of the influencing factors concerned in physiological response to moderate or mild stimuli. Physiological reactions to moderate and mild sensory stimuli may be affected by suggestion in the hypnotic state and by imagination in the normal state. External reactions generally associated with pain may be abolished by suggestion of analgesia under hypnosis, by request to imagine analgesia in the normal waking state, by local block, and by gas anesthesia.

11. Oberst, F.W.: The determination of morphine in the urine of morphine addicts. *Journal of Laboratory and Clinical Medicine* 24:318–329 (1938).

Morphine may be determined quantitatively in concentrations ranging from 0.08 to 3.0 mg per 100 ml urine by a new colorimetric method. The morphine is extracted from the urine by the Pierce and Plant procedure, using the continuous liquid-liquid extraction process followed by acid and alkaline extractions. The final residue dissolved in water is further purified by means of permutit. Morphine combines with permutit, while most other reducing substances are removed by washing. The morphine is finally determined colorimetrically after the addition of sodium carbonate and Folin-Denis phenol reagent to the permutit. The determination of morphine in urine by the diazo reaction has been modified and its limitations discussed. The presence of morphine in the urine of morphine addicts may rapidly be determined by making two extractions with ethyl acetate and the subsequent production of a morphine-molybdate-vanadate complex. A turbidity appears which is roughly proportional to the morphine concentration and may be compared with a prepared standard. Morphine concentrations as low as 0.03 mg in 25 ml of urine can be readily detected. The turbidity produced by the morphine-molybdate-vanadate complex has been developed into a quantitative method for small amounts of morphine extracted from urine by the Pierce and Plant procedure. A nephelometer is used for comparing the unknown turbidity with a standard.

1939

12. Andrews, H.L.: A new electrode for recording bioelectric potentials. *American Heart Journal* 17:599–601 (1939).

13. Himmelsbach, C.K.: Studies of certain addiction characteristics of: (a) dihydromorphine ("paramorphan") (b) dihydrodesoxymorphine-d ("desomorphine") (c) dihydrodesoxycodeine-d ("desocodeine") (d) methyldihydromorphinone ("metopon"). *The Journal of Pharmacology and Experimental Therapeutics* 67:239–249 (1939).

In order to learn something of their respective addiction characteristics (a) dihydromorphine, (b) dihydrodesoxymorphine-d, (c) dihydrodesoxycodeine-d, and (d) methyldihydromorphinone were each substituted for morphine in four successive groups of addicted patients. Addiction satisfaction by the first three drugs was nearly complete. However, with methyldihydromorphinone satisfaction was incomplete and neither slightly larger amounts nor somewhat shorter

intervals of administration improved this. The relative intensities of their dependence effects, as estimated from the corrected amounts of equivalent single doses, and expressed as reciprocals, were: morphine $\frac{1}{50}$, (a) $\frac{1}{14.75}$, (b) $\frac{1}{10.1}$, (c) $\frac{1}{69.9}$, and (d) $\frac{1}{6.9}$. The durations of their dependence effects also varied considerably: morphine 14.4 hours, (a) 19.2 hours, (b) 4.5 hours, (c) 8.5 hours, and (d) 4.5 hours. These variations in intensity and duration of physical dependence effect are undoubtedly the results of alterations in chemical structure. When the components of physical dependence effect and of analgetic action have been identified with particular characteristics of the morphine molecule, it should be possible to vary them so as to produce a drug having a long and strong analgetic action, but a short and weak dependence effect. Such a drug would be ideal for clinical purposes.

14. Williams, E.G.: Blood concentration in morphine addicts. *The Journal of Pharmacology and Experimental Therapeutics* 67:290–298 (1939).

In man morphine addiction with strong physical dependence is associated with blood hydration. During withdrawal there is a temporary decrease in hydration, but a true concentration does not occur. Postaddicts have normal values for cell volume, specific gravity of plasma, and water content of whole blood.

1940

15. Andrews, H.L.: Studies on codeine addiction. III. The effects of codeine on the electrical potentials of the cerebral cortex. *Public Health Reports* Suppl. 158:20–31 (1940).

A consideration of the results described above leads to the following conclusions: (1) During addiction the percentage of occipital alpha rhythm is uniformly high; (2) The administration of the stabilizing injection of either morphine or codeine during addiction increases the alpha percentage and decreases the alpha frequency; (3) The percentage of occipital alpha activity is less during codeine stabilization than during morphine stabilization; (4) There are changes in alpha frequency corresponding to the changes in alpha percentage; (5) Bilateral asynchronism seems to be accentuated by the substitution of codeine for morphine; (6) During withdrawal from codeine, the occipital alpha percentage is usually at least as high as during addiction; (7) A single injection of codeine to a nonaddicted individual (but one who has previously been addicted) produces little change in the brain potentials; and (8) A single injection does, however, increase the time required to block the occipital alpha rhythm.

16. Brown, R.R.: The order of certain psycho-physiological events following intravenous injections of morphine. *The Journal of General Psychology* 22:321–340 (1940).

By means of a modified continuous injection technique, morphine sulphate was administered intravenously in gradually increasing amounts to five volunteer males—three former morphine addicts, and two nonaddicts who were postgraduate students in psychology. Continuous records of respiratory and pulse rates were secured during the administration and subjects were requested to report all sensations and changes in feeling tone. Injections of physiological saline were used as controls. The results were analyzed and discussed with reference to the physiological and experiential changes occurring with gradual increase in dosage, with special emphasis upon time of physiological changes with reference to reported experiential effects. The results indicated the significance of the continuous intravenous injection method as a means of separating the experiential from the physiological effects of morphine. Physiological changes were produced prior to reports of drug effect, the respiration showing the typical decrease, whereas the pulse increased in rate. The two nonaddict subjects did not differ from the three former addicts with respect to directional changes in pulse and respiratory rates following morphine administration. The nonaddicts, however, reported the effects as being disagreeable; whereas the former addicts reported pleasant effects. It was suggested that the action of morphine might be fundamentally excitatory, the depressive actions representing functional changes associated with the operation of compensatory mechanisms.

Under the reported experimental conditions, the following conclusions appear to be justified: (1) With gradual intravenous administration of morphine, an increase in pulse rate may be produced prior to verbal reports of drug effects; (2) With gradual intravenous administration of morphine, a depression of the respiratory rate may be produced prior to report of drug effect; (3) The order of experimental effect following morphine administration does not support Verworn's theory of narcosis; and (4) The continuous intravenous injection method should prove of value in the field of psychopharmacology by allowing for: (a) more adequate control of rate of drug admission into the blood stream; (b) more adequate control of drug concentration in the blood stream; (c) elimination of difficulties involved in the control of sensory cues; and (d) elimination of variables due to individual differences in rates of absorption.

17. Brown, R.R.: The relation of body build to drug addiction. *Public Health Reports* 55:1954–1963 (1940).

On the basis of measurements taken on 400 native, white, male drug

addicts, the following conclusions appear to be justified: (1) The narcotic drug addicts included in this study were average or slightly superior in height and weight; (2) There was an average gain in weight of a little more than 3 kg after 5½ months of institutionalization; (3) The body build of this narcotic drug addict group was found to be within normal limits with a trend toward the pyknic end of the distribution; and (4) The etiology of drug addiction cannot be ascribed in these cases to gross constitutional weakness.

18. Himmelsbach, C.K.: Studies on codeine addiction. I. A review of the literature on codeine addiction. *Public Health Reports,* Supp. 158:1–10 (1940).

This review of the clinical and animal experimental literature shows that, while codeine addiction is certainly not a myth, and in some cases the withdrawal signs and symptoms are as severe as those which follow withdrawal of morphine from morphine addicts, codeine is less addictive than morphine. While codeine would seem to have a peculiarly specific appeal to certain persons, the chief factors which lead to codeine addiction appear to be: (1) Its injudicious use in the practice of medicine; (2) Inadequate legal control; and (3) Difficulty in obtaining the usual addiction drugs. The chief factors which operate to prevent greater incidence of codeine addiction appear to be: (1) Its euphoric effects are of decidedly lower order than either morphine or heroin; (2) The cost of addiction-sustaining amounts of codeine is much greater than for equally effective doses of morphine or heroin; and (3) Its low solubility (4 percent) and necessarily larger dose make the bulk of an effective addiction dose decidedly inconvenient to administer; for example, 5 grains (0.325 g) of codeine would require more than 8 ml of distilled water, whereas 1 grain of morphine can be dissolved easily in 1.25 ml of distilled water. Codeine is certainly liable to cause addiction when used in excessive amounts, or when it is administered to persons whose unstable nervous makeup causes them to become easy victims of the seductive calm produced by opiates.

19. Himmelsbach, C.K.: Thiamine in the treatment of the morphine abstinence syndrome in man. *The Journal of Pharmacology and Experimental Therapeutics* 70:293–296 (1940).

It is believed that additional thiamine would not have caused greater effect, for amounts of thiamine in excess of body needs are destroyed or excreted. In the presence of thiamine deficiency, the blood pyruvic acid rises. A few scattered analyses of blood pyruvic acid made on some of these patients during addiction, before and after thiamine, were all within normal limits. Further consideration of dosage indicates that the amounts of thiamine administered to these patients (2.4 to 17

mg per kg) were comparable to the amounts administered to addicted rats (approximately 20 mg per kg). In view of the failure of thiamine significantly to affect the human abstinence syndrome it would appear that the validity of the rat addiction test of Himmelsbach, Gerlach, and Stanton might be open to question, insofar as comparisons of the responses of the rat and human abstinence syndrome to treatment are concerned. The discrepancy in these results might indicate a difference in the fundamental nature of morphine addiction in rat and man. Thiamine has no significant effect on the human abstinence syndrome.

20. Himmelsbach, C.K. and Andrews, H.L.: Studies on codeine addiction. II. Studies of physical dependence on codeine. *Public Health Reports,* Supp. 158:11–19 (1940).

Codeine administered either subcutaneously or orally supports preestablished physical dependence to morphine when given in amounts about 5.2 times greater than morphine. Satisfaction of physical dependence by codeine is not complete. This is shown by the consistent appearance of mild abstinence phenomena during the course of codeine administration, and by the less severe abstinence syndrome which occurs following withdrawal of codeine. This difference in intensity of the abstinence syndromes of codeine and morphine withdrawal would appear to be due in part to the loss of physical dependence which occurred chiefly in the transition period. The duration of the physical dependence action of codeine was estimated to be 16.2 hours, which is not significantly greater than that of morphine. The comparative intensities of the physical dependence effects of codeine and morphine are $\frac{1}{259}$ and $\frac{1}{50}$ respectively.

21. Oberst, F.W.: Free and bound morphine in the urine of morphine addicts. *The Journal of Pharmacology and Experimental Therapeutics* 69:240–251 (1940).

Morphine excretion studies were made on 352 urine samples from 29 morphine addicts receiving morphine sulfate subcutaneously in daily doses varying from 45 to 4,439 mg. Sixty-two samples from 11 of these patients were boiled for 3 hours in an acid solution before making the morphine extraction. The average daily amount of morphine found in urine before hydrolysis was 8.6 mg, or 4.42 percent of the intake. The percentage excretion was slightly decreased at the higher dosage levels. In some patients receiving morphine subcutaneously and orally it was found that during subcutaneous administration the percentage excretion in urine was higher than during oral administration, the values being 5.74 and 2.69, respectively. The urinary output of morphine on the first day of abstinence markedly decreased and became lower each

succeeding day until by the fifth or sixth day no more was found. The amount of morphine found in urine after hydrolysis was from 3 to 36 times that found before hydrolysis, the higher portions being associated with the higher dosage levels. The existence of a bound morphine in urine from addicts was established.

In conclusion, it is believed that morphine is excreted in the urine in at least two forms, free and bound. The fractional amount of the bound portion is decidedly increased over the free portion at the higher dosage levels. The discovery of bound morphine in the urine of addicts makes it possible to account for a greater percentage of the amount administered than has been possible heretofore. The conception of the existence of a conjugating mechanism serving to detoxify morphine was mentioned.

22. Oberst, F.W.: Studies on codeine addiction. V. Urinary excretion of codeine. *Public Health Reports,* Supp. 158:50–60 (1940).

A gravimetric method for the determination of codeine in urine is described in detail. Morphine and codeine excretion studies were made on eight morphine addicts during morphine administration and following substitution of codeine. The elimination of codeine in the urine of a codeine addict is also reported. During subcutaneous administration of either morphine or codeine, the percentage excretion in urine was higher than during oral administration. There was little difference between the average percentage of morphine and codeine excretion when the drugs were administered subcutaneously, the values being 5.42 and 5.94, respectively. During oral administration the percentage of morphine excreted was a little lower than that of codeine, the values being 2.69 and 4.26, respectively. The average daily amount of codeine excreted in the urine of a codeine addict was 53.5 mg, which is 5.78 percent of the total amount administered orally. Following the withdrawal of morphine and the substitution of codeine, morphine may be excreted for 3 to 5 days, the amount becoming less on each successive day. After withdrawal of codeine the amount present in the urine for the first day was generally low. Frequently no codeine was found on the second day. The urine of the codeine addict was not free from codeine until the fourth day after withdrawal.

1941

23. Andrews, H.L.: Biophysical studies of drug addiction. *Hospital News* 8:14–18 (1941).

24–25. Andrews, H.L.: Brain potentials and morphine addiction. *Psychosomatic Medicine* 3:399–409 (1941).

Brain potential records have been taken on a series of 50 men during maintained addiction to morphine, and on a second series of 50 men whose addiction had been terminated for at least 1 year. Neither group shows alpha percentage distribution curves in agreement with those found by other workers for normal groups. The addiction state is characterized by an abnormally high alpha output. In some cases the high alpha index is maintained following withdrawal, while in others there is a sharp drop. Abnormal rhythms were found in severely addicted patients and these were greatly reduced following withdrawal. In general, a single dose of morphine in a nonaddict had no appreciable effect on the cortical potentials. In one case, however, sleep rhythms were recorded when the patient was definitely not asleep. The high alpha output was maintained during the active phase of withdrawal, in spite of a high degree of emotional tension, a factor which usually abolishes the alpha rhythm.

26. Andrews, H.L. and Workman, W.: Pain threshold measurements in the dog. *The Journal of Pharmacology and Experimental Therapeutics* 73:99–103 (1941).

The results described show that there exists in the dog a mechanism which can be used to measure pain thresholds in a manner quite analogous to that used in man. Drugs affect these thresholds in much the same way as in man and hence it seems that this method should be generally useful for studying the pain mechanism and the action of drugs on it.

27. Brown, R.R.: Psychological investigations in drug addiction. *Hospital News* 8:9–11 (1941).

28. Himmelsbach, C.K.: The effects of certain chemical changes on the addiction characteristics of drugs of the morphine, codeine series. *The Journal of Pharmacology and Experimental Therapeutics* 71:42–48 (1941).

By means of the substitution technique, data were obtained on the potency and duration of physical dependence action of each of 10 related drugs of the morphine-codeine series. From comparisons of pairs of drugs, differing from each other in only one structural respect, it would appear that in so far as physical dependence action is concerned: (a) Methylation of the phenolic OH reduces potency and prolongs action, (b) Replacement of the alcoholic OH by H or O increases potency and shortens the action, (c) Spatial shift of the alcoholic OH results in irregular effects, and (d) Saturation of the C–7, 8 double bond tends to increase both the potency and duration of action. These findings are qualitatively similar to those of Small and Eddy (ref. 1, part I) in so far as the effects of (a) methylation of the phenolic OH and (b)

replacement of the alcoholic OH by H or O are concerned, but are qualitatively somewhat dissimilar to their findings on the effects of (c) spatial shift of the alcoholic OH and (d) saturation of C–7, 8 double bond. The dissimilarities can be considered favorable to the assumption of a dissociation of physical dependence action from other morphine effects. None of the types of chemical modification mentioned in this report caused reductions in both duration and intensity of physical dependence action.

29. Himmelsbach, C.K.: The morphine abstinence syndrome, its nature and treatment. *Annals of Internal Medicine* 15:829–839 (1941).

The morphine abstinence syndrome is a definite clinical entity. Some of the more common signs and symptoms of this syndrome are: yawning, lacrimation, rhinorrhea, perspiration, gooseflesh, tremor, dilated pupils, nervousness, restlessness, aching of legs, anorexia, nausea, abdominal cramps, emesis, diarrhea, insomnia, fever, hyperpnea, elevation of blood pressure, and loss of weight. An adequate program for management of the abstinence syndrome consists of a preliminary period of stabilization, rapid reduction of morphine, harmless supplementary measures such as infusions, sedatives, and flow baths, and good nursing with frequent and careful observation. The most important feature of withdrawal treatment is the judicious use of opiates.

30. Himmelsbach, C.K.: The search for a nonaddictive substitute for morphine. *Hospital News* 8:2–5 (1941).

31. Himmelsbach, C.K.: Studies on the relation of drug addiction to the autonomic nervous system: Results of cold pressor tests. *The Journal of Pharmacology and Experimental Therapeutics* 73:91–98 (1941).

The blood pressure response of addicts to a standard cold stimulus is greater than normal and recovery is slower than normal. This abnormal reaction, suggesting that hyperirritability of autonomic centers is associated with addiction, slowly reverts to normal in both particulars following withdrawal of morphine. The acute effect of morphine in normal persons and in postaddicts is to reduce the blood pressure response to cold and to accelerate recovery. In this, the effect of morphine resembles the action of neither adrenergic nor cholinergic drugs, but is similar to the effect of hypnotics, analgetics, and anesthetics.

32. Oberst, F.W.: Relationship of the chemical structure of morphine derivatives to their urinary excretion in free and bound forms. *The Journal of Pharmacology and Experimental Therapeutics* 73:401–403 (1941).

Morphine, alpha-isomorphine, methyl morphine (codeine), and dihydroheterocodeine are excreted in both free and bound forms.

Diacetylmorphine (heroin) is excreted as morphine in both forms. Dihydrocodeine and dihydroisocodeine are excreted mainly in the free form, only small amounts being bound. Dihydrocodeine methyl ether is excreted only in the free form. These results indicate that conjugation takes place on either the phenolic or the alcoholic hydroxide. Since the glucuronic acid concentration in urine increases proportionately with increasing dosages of morphine, the substance bound with morphine and certain of its derivatives is thought to be largely glucuronic acid or its lactone form, glucurone.

33. Oberst, F.W.: The excretion of morphine in morphine addicts. *Hospital News* 8:11–13 (1941).

34. Oberst, F.W. and Andrews, H.L.: The electrolytic dissociation of morphine derivatives and certain synthetic analgetic compounds. *The Journal of Pharmacology and Experimental Therapeutics* 71:38–41 (1941).

This study found that there is no correlation between analgesic or toxic properties of phenanthrene congeners and either their dissociation consonants or equivalent conductants in dilute solution.

35. Williams, E.G.: Physiological investigations in drug addiction. *Hospital News* 8:5–9 (1941).

1942

36. Andrews, H.L.: Cortical effects of Demerol. *The Journal of Pharmacology and Experimental Therapeutics* 76:89–94 (1942).

Demerol is a drug which has a profound effect on the central nervous system when used in quantities sufficient to satisfy the desires of addicts. These effects are of such a nature that serious harm might come to these who could obtain the drug in quantities sufficient to meet such requirements. If the drug were freely available abuse might occur, for all patients considered most of the effects pleasant and desirable, and stated that the discomforts following withdrawal were sufficient to discourage voluntary discontinuance.

37. Andrews, H.L.: The development of tolerance to Demerol. *The Journal of Pharmacology and Experimental Therapeutics* 75:338–341 (1942).

Using patients previously addicted to morphine, it has been shown that tolerance develops to the pain threshold raising effect of Demerol. The development of tolerance appears to be nearly maximal at the end of 8 weeks. There was no significant change in the preinjection

thresholds. The tolerance is maintained for at least 30 days after the drug has been discontinued.

38. ANDREWS, H.L.: The effect of morphine and prostigmine methylsulfate. *Journal of the American Medical Association* 120:525–527 (1942).

It appears that the combination morphine-prostigmine methylsulfate is not significantly more effective in raising the pain threshold than morphine alone and that the addition of prostigmine methylsulfate does not appreciably change the rate at which tolerance is developed.

39. BROWN, R.R. and PARTINGTON, J.E: The intelligence of the narcotic drug addict. *Journal of General Psychology* 26:175–179 (1942).

On the basis of 371 Wechsler-Bellevue examinations conducted on native, white, male, narcotic drug addicts, the following conclusions appear to be justified: (1) Native, white, male, narcotic drug addicts range in intelligence from defective to very superior, with the largest percentages falling into the average and bright-normal classifications; (2) The addict group shows a lower percentage of cases in defective and in the very superior and superior intelligence classifications as compared with Wechsler's normal group; (3) The volunteer group of patients shows a slight but statistically significant superiority in IQ over prisoner patients; and (4) Narcotic drug addicts do not differ significantly from nonaddicts with respect to the individual functions measured by the Wechsler-Bellevue scale.

40. BROWN, R.R. and PARTINGTON, J.E.: A psychometric comparison of narcotic addicts with hospital attendants. *Journal of General Psychology* 27:71–79 (1942).

Forty-two attendants were matched with a group of narcotic drug addicts (not addicted at time of test) on the basis of age, color, nativity, and intelligence (Wechsler-Bellevue scale), and the two groups were compared with reference to their performance on a variety of tests. No differences were indicated between the two groups with reference to those measures generally employed in the measurement of intelligence. Differences were found in favor of the drug addict group on tests of cancellation of forms, distribution attention, and speed of adding, subtracting, and multiplying simple numbers, all of these being measures of speed of performance. With reference to the control group used (hospital attendants) the addicts were consistently faster, without loss of accuracy. Differences were also found between addicts and attendants on a test of perseveration tendencies, the addicts showing a greater disturbance (as measured by increase in time) when simple addition, subtraction, and multiplication problems were mixed and compared with the time for completing sets of unmixed problems. This finding could not

be explained on the basis of speed level differences. Further research is needed to determine the basis for these differences between attendants and addicts.

41. Himmelsbach, C.K.: Clinical studies of drug addiction. *Archives of Internal Medicine* 69:766–772 (1942).

The results of a longitudinal study of 21 persons addicted to morphine or one of its derivatives from the addicted state through withdrawal to the ninth month of total abstinence indicate: (1) the adjustment of physical functions to morphine addiction, while biologically adequate, is incomplete; (2) Physical recovery from addiction is an irregular process requiring approximately 6 months; (3) A simple measure for the estimation of physical recovery from addiction is weighing the patient at monthly intervals following withdrawal. When no significant increase in weight occurs for 3 successive months, it appears safe to assume that maximum physical recovery has been reached; and (4) The basal metabolic rate of the recovered addict is subnormal.

42. Himmelsbach, C.K.: Studies of the addiction liability of "Demerol" (D–140). *The Journal of Pharmacology and Experimental Therapeutics* 75:64–68 (1942).

When substituted for morphine Demerol partially satisfied the physical dependence established to morphine. On withdrawal, after 10 days of substitution, a definite but mild abstinence syndrome occurred. Physical dependence on Demerol resulted from its regular administration to postaddicts over a period of 10 weeks. The abstinence syndrome which occurred following its withdrawal was milder than the morphine abstinence syndrome but otherwise quite typical. The duration of the physical dependence action of Demerol was considerably shorter than that of morphine. Demerol possesses addiction liability.

43. Himmelsbach, C.K., Oberst, F.W., Brown, R.R., and Williams, E.G.: Studies of the influence of prostigmine on morphine addiction. *The Journal of Pharmacology and Experimental Therapeutics* 76:50–56 (1942).

Prostigmine does not prevent the reproduction of physical dependence on morphine in man; on the other hand, it does not appear to potentiate the physical dependence action of morphine.

44. Oberst, F.W.: Studies on the fate of morphine. *The Journal of Pharmacology and Experimental Therapeutics* 74:37–41 (1942).

A modified method for the microdetermination of morphine in quantities from 0.03 to 0.2 mg by the morphine-molybdate-vanadate procedure has been described. Morphine analyses were made on urine,

feces, saliva, gastric contents, perspiration, bile, and blood from morphine addicts, as well as liver obtained at autopsy on two patients who were addicted at the time of death. Feces, liver, and perspiration contained free morphine; bile contained only bound morphine; urine and gastric contents contained both free and bound morphine; no morphine was found in saliva or blood.

1943

45. Andrews, H.L.: Changes in the electroencephalogram during a cycle of morphine addiction. *Psychosomatic Medicine* 5:143–147 (1943).

The assumption of a cortical excitatory state satisfactorily explains the action of repeated doses of morphine. Morphine acts to depress the cortical excitation but this is not necessarily accompanied by a change in the level of alertness. Tolerance to the cortical depressing effect appears to be developed at quite different rates in different individuals.

46. Andrews, H.L.: The effect of opiates on the pain threshold in postaddicts. *Journal of Clinical Investigation* 22:511–516 (1943).

When the pain threshold raising effect of morphine and its derivatives is tested in postaddicts a variable but greatly reduced response is found. Results with certain derivatives suggest that this reduced response may be somewhat specific. The abnormally low response could be explained by a retained ability to rapidly destroy opiates. The measurements of pain threshold appear to have little connection with the clinical relief of pain, for this is accomplished in the postaddict with little or no increase in the morphine dosage.

47. Andrews, H.L., Oberst, F.W., and Williams, E.G.: An improved damping device for high capacity balances. *Review of Scientific Instruments* 14:22–23 (1943).

48. Andrews, H.L.: Skin resistance changes and measurements of pain threshold. *Journal of Clinical Investigation* 22:517–520 (1943).

In general the skin resistance change produced by the radiant stimulus used in the Hardy-Wolff technique is increased with a subjective report of pain. There are some variations, so this cannot be used as an objective measure of the endpoint. In nonaddicts and in postaddicts, there is a reduction in the skin resistance response following a dose of morphine. There is some reduction following codeine but this is not as pronounced as with morphine. The reduction following Demerol is at least as great as that observed with morphine. Following morphine, the

reduction in skin response is maintained considerably beyond the pain threshold effect. The reduced skin resistance response is probably associated with a reduced pain appreciation, which offers an explanation of the clinical relief of pain in the postaddict.

49. Brown, R.R.: The effect of morphine upon the Rorschach pattern in postaddicts. *American Journal of Orthopsychiatry* 13:339–342 (1943).

Twenty-two postaddict patients who had been abstinent for at least 6 months were given injections of morphine in amounts sufficient to produce the effect desired by each patient. The average dose was 34 milligrams (range 15 to 70). The Rorschach test was administered under morphine and nonmorphine conditions, with half of the group receiving the first test after morphine administration and the retest a month later under nonmorphine conditions. The order of testing was reversed for the other half of the group. It was found that the response total, details, rare details, and human movements were increased. Responses to color were also slightly increased, but the erlebnistypus shifted in the direction of M>C. Neurotic signs were reduced by morphine. Signs of intellectual control, organizational energy, and originality were not affected. It therefore appears that under morphine the personality of postaddicts changes in the direction of introversion in the sense of increased phantasy living, with the attention being directed to inner rather than outer stimuli.

50. Himmelsbach, C.K.: Further studies of the addiction liability of Demerol (1-methyl-4-phenyl-piperidine-4-carboxylic acid ethyl ester hydrochloride). *The Journal of Pharmacology and Experimental Therapeutics* 79:5–9 (1943).

Demerol possesses the liability of producing physical dependence similar to that caused by morphine. In clinical doses the addiction liability of Demerol is less than that of morphine. As an addiction preventive measure, caution and restrictions similar to those involved in the clinical use of morphine should be applied to Demerol.

51. Himmelsbach, C.K.: Morphine, with reference to physical dependence. *Federation Proceedings* 2:201–203 (1943).

In this theoretical paper, it is proposed that morphine affects hypothalamic homeostatic centers with resulting autonomic changes. The body attempts to maintain its homeostatic level and with repeated injections of morphine its ability to offset opiate effects improves, giving rise to physiologic tolerance. The resulting strengthening of adaptive processes to morphine creates a situation where morphine is necessary to maintain homeostasis, and when it is withdrawn a new autonomic imbalance obtains which is manifest as the abstinence syndrome.

52. HIMMELSBACH, C.K. and ANDREWS, H.L.: Studies on modification of the morphine abstinence syndrome by drugs. *The Journal of Pharmacology and Experimental Therapeutics* 77:17–23 (1943).

The morphine abstinence syndrome of moderate intensity is sufficiently uniform from the 24th to the 40th hour to permit reasonably accurate prediction of its course from the 30th to 40th hour from data obtained during the preceding 6 hours. A method is described for measuring the effect of drugs administered at the 30th hour of abstinence as percentage deviations from the expected course of the abstinence syndrome. Results by this method confirm the ineffectiveness of thiamine and indicate that prostigmine, pentobarbital, and atropine in the doses given do not ameliorate abstinence syndrome intensity appreciably. Codeine in 26 mg dosage also was ineffective. Pyridoxine caused a slight but presumably nonsignificant reduction. Diethylaminomethyl-3-phenanthryl carbinol caused a prolonged and probably significant reduction. Significant reductions were caused by 52 and 104 mg codeine; 5, 10, and 20 mg morphine; 100 and 200 mg Demerol; and by 80 mg morphine sulfuric ether. The extent of ameliorative effect increased somewhat with dosage. Prostigmine did not potentiate this effect of morphine. The effect of 20 mg morphine intravenously was greater and more sustained than an equal amount given subcutaneously. While these results confirm the cross effectiveness of drugs structurally or pharmacologically similar to morphine, the dose relationships were not the same as found by substitution. Although this method probably will not be useful for studying the duration of action of drugs, the technique offers a quick method for detecting probable addiction liability of drugs.

53. OBERST, F.W.: A method for the determination of Demerol in urine and results of its application. *The Journal of Pharmacology and Experimental Therapeutics* 79:10–15 (1943).

A method for the determination of Demerol in urine is described. The percent of Demerol excreted in the urine of postaddicts not requiring an analgetic receiving 300 to 800 mg Demerol per day varied between 2.2 and 21.2. The average for 273 analyses was 9.1 percent. Tolerance was not a factor affecting Demerol excretion. The average percent excretion of Demerol after single doses of 100 mg was, after 24 hours, about the same as in patients receiving daily multiple doses varying from 300 to 800 mg. About 72 percent of the total amount of detectable Demerol in urine is excreted within 7 hours after a dose.

54. OBERST, F.W.: Studies on the fate of heroin. *The Journal of Pharmacology and Experimental Therapeutics* 79:266–270 (1943).

In alkaline solution (0.5 M Na_2CO_3 at 26° C.) heroin hydrolyzes

rapidly. Approximately 58 percent of the total sample hydrolyzed (calculated as morphine base) in 2 minutes, and 88 percent in 10 minutes. Calculations made from results of these tests indicate that at least 96 percent of the sample tested was diacetylmorphine hydrochloride. As to the fate of heroin in the human body, evidence is presented indicating that all of the drug is hydrolyzed completely. It is not possible to extract heroin hydrochloride added to urine without causing some hydrolysis. Physical dependence on morphine was satisfied by heroin hydrochloride. The ratio of physical dependence satisfying doses of morphine sulfate and heroin hydrochloride was 2 to 1. On this dosage ratio approximately 7 percent of the administered drugs were excreted in free form and 50 percent in bound form.

55. Wikler, A. and Masserman, J.H.: Effects of morphine on learned adaptive responses and experimental neuroses in cats. *Archives of Neurology and Psychiatry* 50:401–404 (1943).

In 4 out of 5 cats, morphine in doses of approximately 1 mg per kilogram of body weight regularly produced refractoriness to stimuli and diminution in activity, lasting from ½ to 2 hours, after which the animal became more restless and evinced notable distractibility over a period of about 6 to 7 hours. The fifth cat exhibited only the latter type of behavior with this dose of morphine. In all animals learned adaptive responses were greatly affected. The more recently acquired and most complex learned responses disappeared first, and then reappeared last, as the effects of the drug wore off. The disintegration of learned complex responses was usually complete within 10 minutes after injection, while reversal of this process began 3 or 4 hours later in most cases. "Experimental neuroses" were produced by creating an impasse between conflicting motivations of hunger and fear. The complex "neurotic" behavior abated with injection of morphine was replaced by previous adaptive patterns about 5 or 6 hours after the administration of the drug. However, in three of the animals the "neurotic" behavior reappeared in full force after the effects of morphine had worn off further, although a cat which had been made only mildly "neurotic" showed notable diminution in its abnormal reactions the next day. In contrast, an animal with a reprecipitated and severe neurosis showed no improvement with doses sufficiently large to cause its death.

56. Wikler, A., Williams, E.G., and Wiesel, C.W.: Monelemia associated with toxic purpura. *Archives of Neurology and Psychiatry* 50:661–668 (1943).

A case of infection of the blood stream with C. (M.) parakrusei, with associated purpuric lesions in the brain, heart, lungs, kidneys, and subcutaneous and retroperitoneal tissues together with anemia and

uremia, is reported in detail. However, it is not possible to exclude with certainty the possibility that these changes were due to an extraordinarily slow-acting toxic effect of a self-administered overdose of paraldehyde.

1944

57. Andrews, H.L. and Himmelsbach, C.K.: Relation of the intensity of the morphine abstinence syndrome to dosage. *The Journal of Pharmacology and Experimental Therapeutics* 81:288–293 (1944).

Data on the abstinence syndrome intensities of 127 morphine addicts stabilized on doses ranging from 40 to 500 mg per day indicate that a functional relationship exists between the total abstinence syndrome for 7 days (T.A.S.–7) and the stabilization dose. From the form of this function it appears that a maximum T.A.S.–7 would be expected at a daily dose of about 500 mg. The theoretical implications and a practical application are discussed.

58. Cahen, R. and Wikler, A.: Effects of morphine on cortical electrical activity of the rat. *Yale Journal of Biology and Medicine* 16:239–243 (1944).

Small sedative doses of morphine (less than 20 mg per kg) have little or no effect on the cortical electrical activity of the unanesthetized rat. After injection of moderately large doses of morphine (20 to 50 mg per kg) increase in amplitude and decrease in frequency appear early. Somewhat later, periodic "bursts" of 10 to 12 per second waves of high amplitude appear and persist for several hours. These effects are similar to those produced by moderate doses of barbiturates in man and in animals, and the EEG pattern resembles that seen during natural sleep in man. Large doses of morphine (200 mg per kg) or smaller doses (40 to 100 mg per kg) combined with moderate doses of a barbiturate (9 to 30 mg per kg) decrease the amplitude and finally abolish the cortical electrical activity because of marked respiratory depression with resulting anoxia. If anoxia is prevented by artificial respiration, cortical electrical activity returns. The changes produced by morphine in the electrical activity of the cortex of the rat are not specific for this drug and appear to be produced by mechanisms similar to those operating during light or moderate barbiturate narcosis.

59. Himmelsbach, C.K.: Studies on the relation of drug addiction to the autonomic nervous system: results of tests of peripheral blood flow.

The Journal of Pharmacology and Experimental Therapeutics 80:343–352 (1944).

The resting blood flow to the hands of addicts and postaddicts is subnormal, while that of marihuana users is normal. Morphine significantly increases the rate of blood flow to the hand and forearm. The total increase to the hand in the first postinjection hour is greater with 10 and 20 mg than with 40 and 60 mg. The effect on the hand seems to require intact sympathetic nerve control. Demerol increases blood flow to the hand.

60. Himmelsbach, C.K.: Treatment of the morphine abstinence syndrome with a synthetic cannabis-like compound. *Southern Medical Journal* 37:26–29 (1944).

Pyrahexyl compound appears to possess considerable cannabis-like effect when administered orally, but little or none when given intramuscularly. When given by mouth in definitely effective amounts pyrahexyl compound had no appreciable ameliorative effect on the opiate abstinence syndrome.

61. Oberst, F.W. and Gross, E.G.: Studies on the fate of morphine sulfuric ether. *The Journal of Pharmacology and Experimental Therapeutics* 80:188–191 (1944).

The excretion of morphine sulfuric ether, and in some instances its potassium salt, has been studied in 9 nontolerant and 2 tolerant dogs, and in 2 nonaddicts, 1 addict, and 10 postaddicts. It is excreted in urine as both free and bound morphine, the amounts of which are somewhat lower than that reported for morphine per se. Its pharmacological activity is of a low order; it does not produce euphoria in man or relieve pain. Neither can it be substituted for morphine in addicts nor does it relieve withdrawal symptoms. Its pain-threshold raising effect as determined by Hardy, Wolff, and Goodell technique is practically absent in man and is questionable in dogs.

62. Wikler, A.: Studies on the action of morphine on the central nervous system of cat. *The Journal of Pharmacology and Experimental Therapeutics* 80:176–187 (1944).

In the intact cat, small doses of morphine (2 to 5 mg per kg) caused changes in behavior which appear to represent disintegration of adaptive responses. This, in turn, appears to be associated with selective depression rather than with "stimulation" of the nervous system. With larger doses (10 to 15 mg per kg) evidence of delayed stimulant actions ("startle response," muscle twitches, spontaneous running) are superimposed. In acute decorticate and hypothalamic cats, 2–5 mg per kg of morphine depress or abolish the skeletal motor components of

"sham rage," and the righting reflexes, the effects being more marked and prolonged in the decorticate animal. In both, the forelegs become rigidly extended, and tonic neck and labyrinthine reflexes are often demonstrable. With larger doses, the depressant effect is shorter, and may be followed by excitatory effects, especially augmentation of running movements. In acute decerebrate cats, extensor rigidity and the labyrinthine reflexes are not altered by small or moderate doses of morphine. Delayed excitatory effects, such as alternate rhythmic movements of the forelegs, the "startle" response, and acoustic reflex turning of the head occur earlier than in other preparations, and increase in intensity over a period of 4–6 hours. In acute and chronic spinal preparations, the responses to nociceptive stimuli (flexor and crossed extensor reflexes) are markedly depressed, while the responses to stretch (knee and ankle jerks) are either not affected or they are slightly augmented by morphine in the dose range studied. It is concluded that the action of morphine on the somatic central nervous system of the cat may be resolved into (a) selective depression, with consequent release phenomena, and (b) delayed excitatory effects. Theoretical considerations indicate that the ultimate locus of the depressant action of morphine may be on interneurones. The excitability of motoneurones may be enhanced by a reciprocal mechanism secondary to depression of inhibiting internuncial neurones, or they may be stimulated directly. Species differences in the reaction to morphine probably are due, not to hypothetical differences in the action of the drug on nerve cells, but to (a) difference in neural organization, such as the relative preponderance of sympathetic and parasympathetic, facilitating and inhibiting mechanisms, and (b) differences in the concentration of the alkaloid necessary to produce comparable effects.

1945

63. Wikler, A.: Effects of morphine, nembutal, ether and eserine on two-neuron and multineuron reflexes in the cat. *Proceedings of the Society for Experimental Biology* 58:193–196 (1945).

In the spinal cat, small doses of morphine (5 mg per kg) enhanced two-neuron arc reflex discharges and depressed those traversing multineuron arcs. After the injection of larger doses (15 mg per kg), depression of multineuron arc discharges was followed by enhancement of these discharges. Nembutal depressed both two-neuron and multineuron arc discharges. These effects were unaltered by previous injection of eserine or morphine plus eserine, and increased progressively with the dose of nembutal. Ether depressed both two-neuron and mul-

tineuron reflex arc discharges. Eserine enhanced two-neuron arc discharges, but had little effect on multineuron arc discharges. If, however, morphine had been injected previously, resulting in enhancement of two-neuron and depression of multineuron arc discharges, eserine caused enhancement of both types of reflex arc discharges.

64. Wikler, A.: Pain—a discussion of recent progress. *Kentucky Medical Journal* 43:298 (1945).

65. Wikler, A., Goodell, H., and Wolff, H.G.: Studies on pain. The effects of analgesic agents on sensations other than pain. *The Journal of Pharmacology and Experimental Therapeutics* 83:294–299 (1945).

The thresholds of perception of sensations other than pain—touch, vibration, two-point discrimination, smell, and hearing—were not raised by "therapeutic" amounts of morphine sulfate, codeine phosphate, ethyl alcohol (95 percent), a barbiturate ("Evipal") and acetylsalicylic acid.

1946

66. Brown, R.R.: A cycle of morphine addiction. Biological and psychological studies. Part II: Psychological investigations. *Public Health Reports* 61:37–53 (1946).

Psychological and psychophysiological studies were made on two postaddicts before, during, and following the development of tolerance to and dependence on morphine. Both patients were studied every other week over a 2-year period. The following measurements were taken: Johnson code learning, sensitivity to electric current, steadiness, tapping speed, continuous subtraction, Scripture's block oscillations, immediate and delayed recall of nonsense syllables, voice- and hand-response time, and physiological reactions (blood pressure, pulse rate, skin conductance, and respiration) to word stimuli. It was found that addiction to morphine was associated with a reduction in efficiency. The voice- and hand-response time to word stimuli was slowed; improvement in code learning was delayed; and speed of tapping was decreased during the latter stage of addiction in both patients. With the possible exception of steadiness in the case of G, there were no tests which indicated any beneficial effects of morphine addiction upon efficiency. The amplitude of the electrodermal response to word stimuli was significantly reduced following the administration of morphine, whereas the blood pressure response to the same stimuli was increased. No satisfactory explanation of the opposite effects of the electrodermal response

and blood pressure can be offered on the basis of evidence now available, but it was suggested that a release of lower centers from cortical inhibitory control may be involved. The polygraphic data were subjected to statistical analysis to determine the extent to which the various functions gave a differential response to disturbing as compared with nondisturbing word stimuli. Statistically significant differences between indifferent and disturbing words were found for both patients with respect to electrodermal response, respiratory changes, and voice-response time. Morphine decreased the response difference between these two types of word stimuli. The suggestion was made that morphine may act to ameliorate the disturbing effects of emotional stress.

67. Williams, E.G., Himmelsbach, C.K., Wikler, A., Ruble, D.C., and Lloyd, B.J., Jr.: Studies on marihuana and pyrahexyl compound. *Public Health Reports* 61:1059–1083 (1946).

Single- and continued-dose studies were made on subjects who had been accustomed to smoking marihuana and who were serving sentences for violation of the Marihuana Tax Act. Six subjects were studied for periods of from 26 to 31 days on ad libitum doses of the synthetic substance, pyrahexyl compound. At the beginning of the studies there was euphoria, dryness of the mouth, injected sclerae, increased appetite, swollen eyelids, and spontaneous laughter. There was no gross ataxia. Several days after the beginning of the medication the euphoria gave way to a general lassitude and carelessness in personal appearance and tidiness. No adverse behavior was manifested by any of the subjects during the period of medication. During this period pulse and temperature decreased and weight increased, presumably due to lessened activity. Psychological measurements were made with the Rorschach, Wechsler-Bellevue, tapping speed, Minnesota mechanical ability, and memory for digits tests. These showed that comprehension and analytical thinking were made more difficult and an adverse effect was noted in accuracy on those tests which require concentration and manual dexterity. Personality changes in the direction of lessened inhibitions were also observed. Individuals became more spontaneous and more responsive to external stimuli under the influence of pyrahexyl compound. Single doses of pyrahexyl compound (30 and 120 mg) had little effect on the electroencephalogram. During prolonged medication, however, the dominant frequencies were markedly slowed. When the drug was withdrawn one of the patients manifested a panic state and another exhibited a hypomanic reaction. Six patients were allowed to smoke marihuana cigarettes ad libitum for a period of 39 days; the principal early effects were exhilaration and euphoria. However, after several days this was replaced by general lassitude and indifference which resulted in carelessness in personal hygiene and lack of produc-

tive activity. In a subsequent study one patient developed a transient psychotic episode with paranoid reactions after smoking three marihuana cigarettes. The group as a whole showed a tendency to increase in body weight. Plasma volume, blood volume, and thiocyanate fluid volume were not altered in the patients during or following the period of smoking marihuana cigarettes. Psychologic changes were studied with the aid of the Rorschach, revised Stanford-Binet scale (Form L), MacQuarrie test for mechanical ability, Seashore measure of musical talents, and the Muller-Lyer illusion tests. The results were very similar to those produced by pyrahexyl compound. Musical ability was not improved despite a subjective feeling that such improvement occurred. Smoking a few marihuana cigarettes caused no change in alpha frequency of the electroencephalogram, but there was a distinct trend towards lowering of the alpha percentage and increase in recorded muscle activity. These changes were not present during continued daily smoking of marihuana cigarettes. The electroencephalographic changes thus appeared to parallel the observed changes in overt behavior, namely, initial stimulation followed by subsequent diminution of activity. Touch, vibration, two-point discrimination, and smell thresholds were not affected by marihuana, but time estimation was impaired and in 3 out of the 12 subjects auditory acuity was improved. In conclusion, it appears that the changes produced by these drugs are related to lessening of inhibition and removal of restraint. In the majority of the cases observed by us under our experimental conditions, no antisocial acts were manifested. However, it is recognized that in certain social situations, persons who are very poorly adjusted may exhibit antisocial behavior as a result of the effects of marihuana. Although tolerance apparently developed with prolonged use of both pyrahexyl compound and marihuana, the presence of physical dependence was not established.

68. Williams, E.G. and Oberst, F. W.: A cycle of morphine addiction. Biological and psychological Studies. Part I. Biological investigations. *Public Health Reports* 61:1–25 (1946).

A longitudinal approach to the problem of drug addiction, using laboratory methods, was made on two postaddicts. Prior to any morphine injections, certain tests were made to establish norms for these patients. There were given 20-mg doses of morphine sulfate subcutaneously, at weekly intervals, for a period of 2 months. During the next 6 weeks the frequency of the dosage was increased first to two, and then to three per week, after which the drug was administered daily for 5 weeks. It was then discontinued for 3 days and it was found that a slight but definite dependence had developed. Following this, morphine was given four times per day in increasing amounts. One patient was on this

regimen for approximately 1 month and then permanently withdrawn. The other was given multiple doses of morphine daily for 6 months. The dosage was increased by arbitrary increments at intervals of 2 to 5 weeks. The highest dose was 4,440 mg per day. The recovery period was divided into five parts to show progressive changes. The postaddiction period was arbitrarily chosen as beginning with the ninth month of abstinence.

An accurate account of carbohydrates, fat, protein, and water intake for each patient was made each day for periods of 6 days on alternate weeks. Urine and feces were analyzed for water during the corresponding periods.

Clinical observations, including temperature, blood pressure, pulse, and respiration was made three times daily. Nocturnal activity was determined by recording the number and magnitude of movements the patient made in bed from 11 p.m. to 5:30 a.m. Basal metabolism determinations were made from analyses of oxygen and carbon dioxide in expired air and from insensible weight loss.

Blood was analyzed approximately once a month for sodium, potassium, calcium, inorganic phosphorus, protein, carbon dioxide, pH, specific gravity, water, hemoglobin, and cell volume. Body hydration was determined from plasma volume, thiocyanate fluid volume, water content of blood, hemoglobin, and packed cell volume.

The results of this study indicate that morphine addiction is accompanied by increases in: body water, water content of blood, blood sedimentation, carbohydrate intake, and nocturnal activity; and by decreases in: body weight, hemoglobin, packed cell volume, pulse rate, basal metabolism, and diastolic blood pressure.

In order to determine the "acute" effects of morphine, respired gaseous exchange, insensible weight loss, and blood constituents were studied before and after single doses of morphine at various times during the study. The minute volume of respired air, respiratory quotient, and insensible water loss were usually decreased after morphine, especially after large doses. Basal metabolic rate was decreased after large doses. Blood was found to be slightly more concentrated after morphine. There was no indication that addiction alters the action of the drug.

1947

69. Isbell, H.: The effect of morphine addiction on blood, plasma and "extra cellular" fluid volumes in man. *Public Health Reports* 62:1499–1513 (1947).

Hematocrit readings, red cell count, and hemoglobin values of the blood of men are reduced during addiction to morphine. The diminu-

tion in these measurements, although small, is statistically significant. The water content of plasma and cells is unchanged in morphine addiction. The water content of whole blood is increased. The increase in blood water is due to the increased proportion of plasma to cells and not to an increase in the water content of cells or plasma. Plasma volume is not altered in the course of morphine addiction; total blood volume and blood cell mass are reduced. The anemia, which develops during morphine addiction, is slight and probably has no significance in the production of physical dependence. Thiocyanate and "extra-cellular" fluid volume tended to be increased in addiction when the daily dosage of morphine exceeded 500 mg per day.

70. Isbell, H., Wikler, A., Eddy, N.B., Wilson, J.H., and Moran, C.F.: Tolerance and addiction liability of 6-dimethylamino-4-4-diphenyl-heptanone-3 (methadon). *The Journal of the American Medical Association* 135:888–894 (1947).

Tolerance to the following effects of 6-dimethylamino-4-4-diphenyl-heptanone-3 (methadon) have been shown to develop in animals and/or man: analgesia, sedation, miosis, action on certain hindlimb reflexes of chronic spinal dogs, depression of caloric intake, and respiratory and circulatory actions. Strong physical dependence was developed in intact dogs, spinal dogs, and a chronic decorticated dog after 1 or 2 months administration of 1 to 5 mg per kilogram, subcutaneously four times daily. Methadon completely alleviated the morphine abstinence syndrome in man. Either methadon or morphine abolished the methadon abstinence syndrome in dogs. Methadon prevented the appearance of signs of physical dependence in 12 men who had been proved to be addicted to morphine. After withdrawal of methadon from men who had received the drug for 1 to 6 months, or from man after substitution of methadon for morphine, a mild but definite abstinence syndrome ensued which was characterized by complaints of weakness, fatigue, anxiety, abdominal discomfort, anorexia, insomnia, slight fever, elevation of systolic blood pressure, tachycardia, depression of caloric intake, slight loss of weight, and alteration of glucose tolerance curves. Signs of abstinence did not appear until the 3d day, reached maximum intensity on the 5th to 9th day and subsided by the 10th or 12th day. The abstinence was mild and the average intensity in 27 subjects barely reached significant levels (20 points) when scored by the Himmelsbach point system. Definite evidence of euphoria and of satisfaction with subjective effects produced by the drug was seen after the administration of doses of 10 mg or more to former morphine addicts. Euphoria has rarely been seen in patients not previously addicted to morphine, when methadon was used for the relief of clinical pain. Mild signs, possibly indicative of developing physical dependence, have been seen in 2 cases on temporary abrupt withdrawal of methadon after its administration

for relief from pain in cancer for at least 35 to 40 days. These signs did not become more severe on withdrawals in these same cases after more prolonged administration. Seventeen other patients subjected to methadon medication for 3 weeks to 6 months have shown no evidence of dependence. It is the unanimous opinion of all who have been concerned with the evaluation of the addiction liability that methadon, like morphine, is dangerous with respect to habituation. Since persons with known narcotic experience get a satisfactory subjective reaction from the drug; since the drug suppresses completely the morphine abstinence syndrome; since it can be substituted satisfactorily for morphine in cases of known morphine addiction; and since it produces, in our opinion, a real, however mild, withdrawal picture, methadon must be classed as an addicting drug. We believe that unless the manufacture and use of methadon are controlled, addiction to it will become a serious public health problem.

71. Wikler, A.: Effects of pitressin hydration on the electroencephalogram: Paroxysmal slow activity in nonepileptic patients with previous drug addiction. *Archives of Neurology and Psychiatry* 57:78–84 (1947).

The electroencephalograms of 14 nonepileptic men with previous drug addiction were studied before and after pitressin hydration. No clinical seizures were induced by this procedure. The alpha frequency showed a tendency to slowing after hydration, but in only three instances was the degree of change greater than that which could be expected from day to day variation. There was no significant change in the percentage of alpha activity. In half the records there was a shift to the slow side of the frequency spectrum. In half the records paroxysmal slow activity of moderately high amplitude appeared after hydration. There was some correlation between the appearance of paroxysmal slow activity and the shift of the frequency spectrum to the slow side, but no correlation with the degree of hydration or the amount of pitressin administered. The possible significance of these observations in their relation to idiopathic epilepsy is discussed.

1948

72. Isbell, H.: Methods and results of studying experimental human addiction to the newer synthetic analgesics. *Bulletin of the New York Academy of Sciences* 51:108–122 (1948).

In assessing the addiction liability of a new analgesic drug, attention should be given to all three of the characteristics of addiction to the opiate drugs—tolerance, physical dependence, and habituation (emotional or psychic dependence). Physical dependence and emotional de-

pendence are equally important. The final tests of addiction liability must be carried out on human subjects. Addiction-liability tests which simulate conditions of abuse are more important than tests of addiction liability under conditions of medical use. Four methods of testing addiction liability are described: administration of single doses for the detection of euphoria; the effect of single doses on abstinence from morphine; substitution of the new drug for morphine in cases strongly addicted to morphine; and direct addiction to the new drug. Racemic methadone, levomethadone, and racemic isomethadone are addicting drugs. The total addiction liability of racemic methadone (or levomethadone) is nearly equal to the addiction liability of morphine. The addiction liability of racemic isomethadone is about equal to that of codeine.

73. Isbell, H.: The newer analgesic drugs. Their use and abuse. *Annals of Internal Medicine* 29:1003–1013 (1948).

The pharmacology, addiction liability and clinical use of three new analgesic drugs—metopon, meperidine, and methadon—have been discussed. Metopon and methadon (in repeated dosage) are as effective in relieving pain as is morphine. Metopon produces fewer side reactions than morphine. Methadon causes just as many side reactions as does morphine. Meperidine prevents spasm of smooth muscle in man, and can often be used in subjects who do not tolerate morphine well, but it is less reliable than the other three drugs. All three drugs are addicting. The same precautions should be exercised in their use as are followed in prescribing morphine. Morphine remains the drug of choice for most conditions requiring quick relief of pain for short periods of time. Meperidine is indicated in cases of pain associated with spasm of smooth muscle, or in persons who do not tolerate morphine well. Metopon is limited to oral use in chronic painful diseases. Methadon can be used in most instances in which morphine is indicated. It is particularly useful in cases requiring pain relief for long periods of time, and for withdrawing drugs from patients addicted to the opiates.

74. Isbell, H.: Book review: Lindesmith, Alfred R.: *Opiate Addiction.* Bloomington, Ind.: Principia Press, Inc. 1947. pp. 238. *The Journal of the American Medical Association* 137:1342 (1948).

75. Isbell, H. and Eisenman, A.J.: The addiction liability of some drugs of the methadon series. *The Journal of Pharmacology and Experimental Therapeutics* 93:305–313 (1948).

Methadol and dextromethadon do not produce euphoria in postaddicts and will not relieve abstinence from morphine. Levomethadon produces euphoria in postaddicts, relieves abstinence from morphine, and suppresses signs of physical dependence when substituted for morphine in cases strongly addicted to morphine. Following withdrawal of

levomethadon, after substitution for morphine, an abstinence syndrome develops which is identical with the syndrome of abstinence from racemic methadon. I vomethadon accounts for all the addiction liability of racemic methadon. Isomethadon in sufficient dose intravenously produces euphoria in postaddicts, relieves abstinence from morphine, and partially suppresses signs of abstinence when substituted for morphine in cases addicted to that drug. Following withdrawal of isomethadon, after substitution for morphine, or after direct addiction of former morphine addicts to isomethadon for 42 to 59 days, an abstinence syndrome develops very rapidly. The isomethadon abstinence syndrome resembles abstinence from morphine more than abstinence from methadon. Isomethadon is an addicting drug.

76. Isbell, H., Eisenman, A.J., Wikler, A., and Frank, K.: The effects of single doses of 6-dimethylamino-4-4-diphenyl-3-heptanone (Amidone, methadon or 10820) on human subjects. *The Journal of Pharmacology and Experimental Therapeutics* 92:83–89 (1948).

Five mg subcutaneous doses of amidone elevated the pain threshold of nonaddicts and former morphine addicts as much as 10–15 mg of morphine sulfate. Respiratory rate, pulse rate, rectal temperature, and systolic blood pressures were lowered by amidone. Doses of 10–30 mg of amidone subcutaneously had no significant effect on the electrocardiogram; 60–75 mg of amidone in divided doses had no significant effect on the blood sugar of former addicts; and 30–75 mg of amidone always produced sedation in former morphine addicts. The electroencephalographic pattern was sometimes shifted to the slow side after 30-mg doses; 30 mg, or more, of amidone subcutaneously regularly produced euphoria in former morphine addicts; and 10-30 mg doses intravenously induced intense euphoria. Narcotic drug addicts would abuse amidone if it were freely available.

77. Isbell, H. and Vogel, V.H.: Drug addiction. *Merck Manual* (ed. 8), Rahway, N.J.: Merck & Company (1948).

78. Isbell, H., Vogel, V.H., and Chapman, K.W.: Present status of narcotic addiction, with particular reference to medical indications and comparative addiction liability of the newer and older analgesic drugs. *The Journal of the American Medical Association* 138:1019–1026 (1948).

Because of vigorous enforcement of the Harrison Narcotic Act and treatment of addicts in Federal facilities the total number of narcotic drug addicts in the United States has declined from 150,000 to 200,000 in 1914 to approximately 48,000 at the present time. Drug addiction is a state in which a person has lost the power of self-control with reference to a drug and abuses the use of the drug to such an extent that the person or society is harmed. The drugs to which addiction commonly occurs in the United States are opium and the opium alkaloids, the synthetic

morphinelike analgesics, the barbiturates, bromides, alcohol, marihuana, cocaine, amphetamine and, rarely, peyote. The characteristics of addiction to these drugs are discussed. Drug addiction is primarily a psychiatric problem and should be regarded as a symptom of a basic underlying personality maladjustment. The common personality types of drug addicts are described. The diagnosis of narcotic addiction is usually easy, but may be difficult. Isolation of the patient and observation for signs of abstinence are, at times, the only conclusive means of diagnosis. Withdrawal of drugs is the first and the least important step in the treatment of narcotic addiction. Withdrawal of morphine is best achieved by a 10-day reduction of morphine or by substitution and reduction of methadon. Institutional therapy is necessary for the successful treatment of addiction. A minimum period of treatment of 4 to 6 months is essential. The patient's entire personality must be reoriented by appropriate psychotherapeutic technics. The pharmacologic characteristics, the advantages and disadvantages, and the comparative addiction liabilities of the older and newer analgesic drugs are discussed. The prevention of drug addiction involves the development of an emotionally sound people through the program of the National Mental Health Act, the reduction of the illegitimate use of narcotics by the control measures provided for under the Harrison Narcotic Act, the isolation and treatment of addicts, which prevents them from spreading addiction, and proper cautious use of addicting drugs by physicians.

79. Isbell, H., Wikler, A., Eisenman, A.J., Daingerfield, M., and Frank, K.: Liability of addiction to 6-dimethylamino-4-4-diphenyl-3-heptanone (methadone, "amidone," or "10820") in man. *Archives of Internal Medicine* 82:362–392 (1948).

Methadon relieved the symptoms of abstinence from morphine. Methadon prevented the appearance of signs of physical dependence when substituted for morphine at a level of 1 mg of methadon for each 4 mg of the stabilization dose of morphine. Once substitution was effected, the dose of methadon could be rapidly reduced without signs of abstinence appearing. After withdrawal of methadon, which had been substituted for morphine, a definite abstinence syndrome appeared which was slower in onset and milder in intensity than the syndrome of abstinence from morphine. Fifteen volunteers who were former morphine addicts were given methadon to produce addiction for 28 to 186 days. The psychologic changes and the general behavior of the subjects resembled those seen during morphine addiction. No serious toxic effects were noted even though the dosage was increased to 400 mg daily in some cases. A mild normocytic nonprogressive anemia developed in five cases after 3 months of addiction. Fasting blood sugar content and intravenous dextrose tolerance tended to be low during addiction. Inflammation, induration, and hypesthesia developed in the skin over the

injection sites. Electroencephalographic patterns were slowed. All the men showed evidence of sedation when four doses of 10 mg or more were given daily. The sedative action appeared to be cumulative. Systolic blood pressure, respiratory rates, and pulse rates were depressed throughout addiction. Rectal temperatures were decreased early in addiction and increased thereafter. Tolerance to the following effects of the drug developed as addiction progressed: pain-threshold-elevating action, sedative action, effect on the electroencephalogram, miotic action, depression of caloric intake, and probably circulatory and respiratory actions. After abrupt withdrawal of methadon, a definite abstinence syndrome ensued which was characterized by complaints of weakness, fatigue, anxiety, vague abdominal discomfort, anorexia, insomnia, slight fever, elevation of systolic blood pressure, tachycardia, depression of caloric intake, slight loss of weight, and alteration of glucose tolerance curves. Signs of abstinence did not appear until the 3d day, reached maximum intensity on the 6th day and had not subsided completely at the end of the 14th day. The average intensity of symptoms of abstinence, as measured by the Himmelsbach scoring system, was mild. The syndrome of abstinence from methadon differed from the morphine abstinence syndrome in that few signs of autonomic dysfunction were observed, the onset of abstinence was slower, the intensity was milder and the course was prolonged. Electroencephalograms did not return to normal for 2 to 5 days after withdrawal. The following evidence for the development of habituation (emotional dependence) to methadon was observed: euphoria after repeated small doses (or single large doses), behavioristic and psychologic changes resembling those in morphine addiction, requests for increases in dosage during addiction, requests for methadon following addiction, and preference for methadon over all other drugs. Methadon is an addiction-producing drug. The same precautions should be observed in prescribing methadon as are used in prescribing morphine.

80. Wikler, A.: Neurophysiological aspects of methadone addiction. *Proceedings of the Post-Graduate Institute in Psychosomatic Medicine and Mental Hygiene,* U.S. Public Health Service Hospital, Lexington, Ky. pp. 105–115. (1948).

81. Wikler, A.: Book review: Lindesmith, Alfred R.: *Opiate Addiction.* Bloomington, Ind.: Principia Press, Inc. 1947. Pp. 238. *American Journal of Psychiatry* 105:74–75 (1948).

82. Wikler, A.: Recent progress in research on the neurophysiologic basis of morphine addiction. *American Journal of Psychiatry* 105:329–338 (1948).

83. Wikler, A. and Daingerfield, M.: Practical use of the Rorschach test. *Diseases of the Nervous System* 10:42–45 (1948).

84. Wikler, A. and Frank, K.: Effects of electroshock convulsions on chronic decorticated cats. *Proceedings of the Society for Experimental Biology and Medicine* 67:464–468 (1948).

The effects of single and repeated convulsions induced by electroshock were observed in six chronic decorticated cats. The seizures were characterized by a posture of general semiflexion with small amplitude rapid rhythmic movements of the limbs, jaws and facial musculature, interrupted by one or more short quiescent periods, terminating in running movements after which a more prolonged quiescent phase preceded recovery. Apnea occurred during the seizures and was followed by transitory hyperpnea. Body temperature and pulse rate were not affected significantly. Righting reflexes returned a few minutes after each seizure. Licking reflexes were abolished for from ½ to 3½ hours after each convulsion in three preparations. Sham rage in response to a non-nociceptive stimulus was unaffected or enhanced temporarily after each electroshock convulsion. Sham rage responses (chiefly faciovocal) to nociceptive pressure stimuli applied to the tail were markedly reduced or abolished for from 1 to 2½ hours after each electrically induced seizure. No changes other than those noted after single electroshocks were noted after repeated electrically induced convulsions. The electroencephalographic patterns of electroshock convulsions in the decorticated preparations were characterized by bursts of relatively high voltage 2 to 21 per second rhythms separated by short silent intervals, frequently terminating in a steady 15 to 18 per second discharge before cessation of electrical activity. Slow and fast wave sequences appeared at times during the paroxysmal discharges and were more prominent in previously morphinized preparations. Gross and microscopic studies of the remaining brains after completion of the experiments revealed no changes which could be ascribed to the electric currents used to evoke convulsions.

85. Wikler, A. and Frank, K.: Hindlimb reflexes of chronic spinal dogs during cycles of addiction to morphine and methadone. *The Journal of Pharmacology and Experimental Therapeutics* 94:382–400 (1948).

Methods for preparing long-surviving, chronic spinal dogs, and methods for recording spontaneous activity and hindlimb reflexes in such preparations are described. In chronic spinal dogs, single doses of morphine or methadon depress markedly the ipsilateral flexor and crossed extensor reflexes, enhance the ipsilateral extensor thrust in most instances, and have small but variable effects on the knee jerk. After very large doses of morphine (100–150 mg/kg) or methadon (40–50 mg/kg) tonic and clonic convulsions appear in the segments rostral to the transection but not below it. During addiction to morphine or methadon, tolerance develops to the depressant effects of morphine and methadon on the ipsilateral flexor and crossed extensor reflexes,

but not to the excitant effects on the ipsilateral extensor thrust. As addiction is continued, the preinjection values of the ipsilateral flexor and crossed extensor reflexes increase, both with respect to amplitude and duration of the response. After abrupt cessation of morphine or methadon, the ipsilateral flexor and crossed extensor reflexes continue to increase in magnitude, while the knee jerk and ipsilateral extensor thrusts diminish markedly. Spontaneous rhythmic activity appears in the hindlimbs (dog in lateral recumbent position) as early as 30½ hours after withdrawal of morphine and 9 hours after withdrawal of methadon. This activity increases in magnitude and frequency until a peak is reached about the 72d–90th hour after morphine and about the 24th–30th hour after methadon withdrawal, following which there is a gradual return of the hindlimbs to the preaddiction status over a period of 10–14 days. However, hyperactivity of the ipsilateral flexor reflex may persist for as long as 4 months after withdrawal of morphine. After withdrawal of morphine or methadon, general signs of abstinence such as restlessness, tremors, fever, yawning, vomiting, lacrimation, rhinorrhea, and occasionally diarrhea appear at about the same time as the spontaneous activity in the hindlimbs. These general signs also reach a peak at about the same time as the hindlimb spontaneous activity, but they subside much more rapidly than the changes in reflexes which occur during the withdrawal period. The effects of sodium pentobarbital, neostigmine, eserine, and elevation of body temperature on the hindlimbs of chronic spinal dogs are described. The data are discussed with reference to the problems of loci of action of morphine and methadon, theories of physical dependence, and studies of physical dependence-producing liability of drugs.

1949

86. Isbell, H.: Addiction liability of some derivatives of meperidine. *The Journal of Pharmacology and Experimental Therapeutics* 97:182–189 (1949).

In sufficient dose, bemidone, keto-bemidone, Nu-1196, and Nu-1932 induce morphinelike euphoria in former morphine addicts, and relieve abstinence from morphine. All these compounds must be regarded as addictive. Volunteers experimentally addicted to keto-bemidone exhibited morphinelike regressive behavior and developed tolerance to a number of actions of the drug. Following withdrawal of keto-bemidone, an abstinence syndrome, qualitatively similar to abstinence from morphine but quantitatively more severe, appeared very rapidly. Keto-bemidone has very great addiction liability.

87. Isbell, H. and Vogel, V.H.: The addiction liability of methadon (amidone, dolophine, 10820) and its use in the treatment of the morphine abstinence syndrome. *American Journal of Psychiatry* 105:909–914 (1949).

The addiction liability of methadone was studied in addict volunteers. Methadone produced morphinelike effects, including euphoria in doses of 30–60 mg subcutaneously or 20–30 mg intravenously. In direct addiction experiments 15 nontolerant addicts were given four doses of methadone daily for 28–186 days. The daily total dosage was increased gradually to as much as 400 mg daily in some patients. Definite tolerance to sedative and other effects developed but required longer than tolerance to morphine. On abrupt withdrawal of morphine, definite abstinence developed but was slower in onset than abstinence from morphine, less severe in terms of Himmelsbach's point score method but was more protracted than abstinence from morphine. Methadone reduces the intensity of abstinence from morphine. Methadone completely suppressed signs of abstinence from morphine in 12 patients strongly dependent on morphine. When methadone was withdrawn after substitution for morphine definite abstinence occurred which was slower to appear and less severe than abstinence from morphine. Substitution of methadone for morphine followed by rapid reduction of the methadone is an excellent method of withdrawing morphine from physically dependent patients. The addiction liability of methadone is equal to that of morphine so precautions equal to those followed in the clinical use of morphine should be followed in the clinical use of methadone.

1950

88. Fraser, H.F. and Isbell, H.: Addiction liabilities of morphinan, 6-methyldihydromorphine and dihydrocodeinone. *The Journal of Pharmacology and Experimental Therapeutics* 100:128–134 (1950).

In sufficient dose, morphinan, 6-methyldihydromorphine, and dihydrocodeinone induce morphinelike euphoria in former morphine addicts. Dihydrocodeinone is very effective in relieving signs of abstinence from morphine. 6-Methyldihydromorphine is relatively ineffective in abolishing the objective signs of abstinence from morphine but, in high doses, relieves the subjective complaints associated with withdrawal of morphine. During experimental chronic administration of all three drugs to former morphine addicts, partial tolerance to the sedative action was observed and, in all three instances, morphinelike regressive behavior appeared. Definite signs of abstinence were observed after withdrawal of all three drugs. These were most severe after withdrawal of morphinan, less severe following withdrawal of dihydrocodeinone, and were mild after withdrawal of 6-methyldihydromorphine. Morphi-

nan, 6-methyldihydromorphine, and dihydrocodeinone all possess addiction liability.

89. Isbell, H.: Addiction to barbiturates and barbiturate abstinence syndrome. *Annals of Internal Medicine* 33:108–121 (1950).

Chronic intoxication with barbiturates is a true addiction. The same phenomena observed in addiction to narcotics are also present in chronic barbiturate intoxication—tolerance, emotional dependence, and physical dependence. The symptoms and signs of maintained chronic barbiturate intoxication include impairment of mental ability, confusion, regression, emotional instability, nystagmus, dysarthria, adiadokokinesis, tremor, hypotonia, ataxia in gait and station, and depression of the superficial abdominal reflexes. A characteristic train of symptoms follows abrupt withdrawal of barbiturates from chronically intoxicated persons. The barbiturate abstinence syndrome is characterized by diminution of signs of intoxication which is followed by weakness, tremor, insomnia, great anxiety, anorexia, nausea and vomiting, rapid weight loss, elevation of pulse and respiratory rates, increase in blood pressure, difficulty in making cardiovascular adjustments on standing, convulsions of grand mal type, and the development of a psychosis. The delirium observed in the withdrawal of barbiturates resembles alcoholic delirium tremens and is characterized by anxiety, agitation, fever, insomnia, confusion, disorientation chiefly in place and time but not in person, delusions, and auditory and visual hallucinations. Recovery from chronic barbiturate intoxication and the barbiturate abstinence syndrome is complete so far as can be determined by clinical means and by psychometric testing. Abrupt withdrawal of barbiturates from addicted persons is contraindicated. The only method of withdrawal which is known to be safe involves careful, slow reduction of the dosage of barbiturates.

90. Isbell, H.: Manifestations and treatment of addiction to narcotic drugs and barbiturates. *Medical Clinics of North America* 34:425–438 (1950).

Drug addiction is a condition of chronic intoxication, usually based on a psychiatric disorder, in which a person abuses a drug to such an extent that harm is produced to the individual, to society, or to both, and which is condemned by the society in which the addiction occurs. The important addicting drugs in the United States are morphine and related compounds, the synthetic analgesics (methadone and meperidine), the barbiturates and other sedative drugs, marihuana, cocaine, and amphetamine. The manifestations of addiction to narcotic drugs and to barbiturates have been described. Treatment of drug addiction consists of appropriate type of withdrawal of the particular

drug or drugs used followed by a long period of rehabilitative and psychiatric therapy. Withdrawal of opiates or similar drugs is best effected by the gradual substitution of methadone for whatever drug the patient has been using, followed by reduction of methadone over a period of about 2 days. Withdrawal of barbiturates is best effected by gradual reduction of barbiturates. This is designed to prevent the appearance of a severe abstinence syndrome which is characterized by anxiety, weakness, tremor, insomnia, convulsions, and/or a psychosis resembling alcoholic delirium tremens.

91. Isbell, H., Altschul, S., Kornetsky, C.H., Eisenman, A.J., Flanary, H.G., and Fraser, H.F.: Chronic barbiturate intoxication. An experimental study. *Archives of Neurology and Psychiatry* 64:1–28 (1950).

Five former morphine addict males were given increasing doses of pentobarbital, secobarbital, or amobarbital finally attaining doses of 1.3–1.8 g daily (pentobarbital, secobarbital) or 3.8 g daily amobarbital. Initially patients were drunk. Partial tolerance developed in all cases. Abrupt withdrawal of barbiturates was followed by anxiety, weakness, postural hypotension, tremors, hyperreflexia, convulsions, and a delirium. Recovery was complete. Addiction to barbiturates is more dangerous than addiction to morphine.

92. Isbell, H. and Fraser, H.F.: Addiction to analgesics and barbiturates. *The Journal of Pharmacology and Experimental Therapeutics* 99:355–397 (1950).

A review article concerning the pharmacology, physiology, biochemistry, and clinical features of opioid and barbiturate addiction as they were understood in 1950.

93. Vogel, V.H. and Isbell, H.: Medical aspects of addiction to analgesic drugs. *Bulletin on Narcotics* 2:31–40 (1950).

This clinical paper discusses the etiology, clinical manifestations, diagnosis and treatment of opiate, and opioid addiction. The neurophysiology of physical dependence is discussed as are the psychiatric theories of chronic opiate use.

94. Wikler, A.: Adaptive behavior in long surviving dogs without neocortex. *Archives of Neurology and Psychiatry* 64:29–41 (1950).

The postoperative life histories of two decorticated dogs, one surviving 19 and the other 12 months, are presented. Anatomic studies of the brains in these animals revealed no traces of remaining neocortex. The dogs showed spontaneous changes in the direction of better adaptation with increasing postoperative age in connection with swallowing food, avoiding the walls of their circular pens, extricating themselves

from corners, escaping from the grasp of the attendant and attempting to escape from the pen. On the other hand, the preparations showed no recognition of food, food receptacles, the attendant who always fed them, or the needle prick which always preceded clyses with saline solution and which regularly evoked rage. Formal attempts to produce conditioned motor responses to visual and auditory stimuli, either by the classic pavlovian method or by avoidance technics, were not successful. Discrete conditioned motor responses to tactile stimuli were established after prolonged efforts. During attempts to produce conditioned salivation associated with injections of morphine, salivation was observed only as part of a generalized rage response before injection of the drug. Attempts to produce time conditioning of increased motor activity were not successful. An unconditioned tactile salivatory response was observed which was intensified by hunger and diminished by feeding. After complete decortication, one of the dogs (an adult male) reverted to the female posture during urination. Decortication did not alter the pattern of the reaction of the dogs to electrical stimulation of the pulp nerves of teeth; the threshold of such reactions appeared to become elevated slightly after the operation. These observations are discussed with reference to the problem of adaptation and conditioning.

95. Wikler, A.: Sites and mechanisms of action of morphine and related drugs in the central nervous system. *The Journal of Pharmacology and Experimental Therapeutics* 2, Part II:435–506 (1950).

96. Wikler, A. and Altschul, S.: Effects of methadone and morphine on the electroencephalogram of the dog. *The Journal of Pharmacology and Experimental Therapeutics* 98:437–446 (1950).

The effects of small and large doses of methadone and morphine on the electroencephalogram were studied in unanesthetized and uncurarized dogs and in curarized dogs. The motor pattern of the convulsive seizures induced by large doses of these drugs was also observed in different dogs. A "mercury cup" electrode is described which facilitates the repeated recording of electroencephalograms from the dura over the cerebral cortex in unanesthetized and uncurarized animals, without interference due to artifacts from the scalp and temporal muscles. Small doses of methadone or morphine produce an admixture of fast and high voltage slow activity in cortical tracings alone. The seizure discharges from cortical tracings were both of the spike and dome and sustained spike patterns. At times the former passed over into the latter without interruption. An "after-seizure" 25-per-second low voltage discharge in the tracings from the sphenoid lead was not associated with activity in the cortical leads. The motor pattern of seizures induced in dogs by large doses of methadone or morphine were essentially the same, although

clonic movements were more prominent in the methadone convulsions. These seizures appeared much sooner after subcutaneous injection of methadone than after morphine.

1951

97. Altschul, S. and Wikler, A.: Electroencephalogram during a cycle of addiction to keto-bemidone. *Electroencephalography and Clinical Neurophysiology* 3:149–153 (1951).

The effects on the electroencephalogram of single and repeated doses of the potent synthetic analgesic agent, keto-bemidone, were studied in five men. Single doses of 20.0 to 30.0 mg of the drug produced no effect on the electroencephalograms except for a drop in mean alpha frequency, which occurred in 4 out of 10 records. During an addiction period of about 60 days, during which a dose level of 290.0 to 450.0 mg was maintained, more or less continuous slow activity appeared in the records of all subjects, and in three there was a concomitant increase in fast activity at the expense of the middle range. Clinically, the subjects were sedated and somnolescent, but the clinical effects could not be correlated quantitatively with the severity of the changes in the electroencephalograms. In two subjects with abnormal control electroencephalograms, paroxysmal high voltage slow, and spike and dome activity appeared early during addiction, but were not noted again later in the addiction period. No clinical seizures were observed. During the height of the abstinence syndrome after abrupt withdrawal of keto-bemidone, slow activity reappeared in the electroencephalogram. In the subjects who exhibited paroxysmal activity during addiction, paroxysmal high voltage slow and also bursts of high voltage 18-cycles-per-second activity appeared in the electroencephalograms during the withdrawal period, without overt seizures. The relation of these findings to the physiological basis of the abstinence syndrome is discussed. The particular danger of the continued use of this drug by persons with subclinical or overt epilepsy is stressed.

98. Houde, R.W. and Wikler, A.: Delineation of the skin-twitch response in dogs and the effects thereon of morphine, thiopental and mephenesin. *The Journal of Pharmacology and Experimental Therapeutics* 103:236–242 (1951).

Anatomic and physiologic studies indicate that the skin-twitch response to nociceptive stimulation in the dog is integrated over a spinal reflex arc whose afferent limb arises from the cutaneous innervation of portions of about T–2 to L–7 dermatomes (corresponding roughly to

the receptive zone of the scratch reflex), and whose efferent limb traverses mainly the C–8 ventral root, innervating the cutaneous maximus muscle through the external thoracic nerve. The amplitude of the skin-twitch response is enhanced by section of the spinal cord at appropriate levels. Morphine, in doses of 5 and 10 mg/kg, depresses the skin-twitch response in both intact and spinal dogs, but to a greater degree in the former. The depressant effects of morphine on the skin twitch in intact dogs is due partly to a direct spinal cord depressant action, and partly to augmentation of supraspinal inhibitory mechanisms. The effects of morphine on the skin twitch in dogs are nonspecific since this response is also depressed by adequate doses of thiopental or mephenesin. The effects of depressant drugs on the amplitude of reflex responses to supramaximal stimuli are more reliable indices of their effectiveness than are prolongations of time required for a constant stimulus, or elevations of intensities of stimuli of fixed duration, to elicit "threshold" responses. The connotations of the term "threshold" when used in connection with such measurements are different from those which are implied in electrophysiology. The significance of these findings is discussed briefly with reference to the general validity of current analgesic testing methods in animals.

99. Houde, R.W., Wikler, A., and Irwin, S.J.: Comparative actions of analgesic, hypnotic and paralytic agents on hindlimb reflexes in chronic spinal dogs. *The Journal of Pharmacology and Experimental Therapeutics* 103:243–248 (1951).

Characteristic changes in the pattern of hindlimb reflexes in chronic spinal dogs are observed after administration of potent analgesic (morphine and methadone), hypnotic (thiopental and pentobarbital) and paralytic (mephenesin and benzimidazole) agents. When the ipsilateral flexor, crossed extensor and Philippson's reflexes were depressed markedly by adequate doses of these drugs, the ipsilateral extensor thrusts were enhanced by the analgesics and depressed by the other agents. Concomitantly, the knee jerks were enhanced by the paralytic compounds, depressed by the hypnotics and were affected slightly and variably by the analgesics under the conditions of our experiments. After administration of 100 mg/kg of morphine, the ipsilateral flexor reflex was depressed and the ipsilateral extensor thrust, enhanced. These effects persisted for several days, after which the ipsilateral flexor reflex became hyperactive, while the ipsilateral extensor thrust was reduced in magnitude. These "rebound" effects were partially reversed by an additional dose of as little as 1 mg/kg of morphine. Such changes resemble those which occur in the hindlimbs of chronic spinal dogs after abrupt withdrawal of morphine following a period of addiction to smaller doses of the drug. The specificity of the

changes in pattern of hindlimb reflexes in chronic spinal dogs which are produced by single doses of analgesic, hypnotic, and paralytic agents may serve as a more reliable basis for classifying new compounds than the use of any single reflex, either in intact or in spinal animals. The proper place of studies on spinal animals in research on the mechanisms of drug action is discussed.

100. Isbell, H.: Acute and chronic barbiturate intoxication. *Veterans Administration Technical Bulletin,* TB 10–76 (1951).

A review article concerning clinical manifestations, pathophysiology and treatment of acute and chronic barbiturate intoxication as understood in 1951. Supportive treatment is stressed in acute barbiturate intoxication. Chronic barbiturate intoxication causes a type of physical dependence manifest by convulsions and a delirium after abrupt withdrawal. These serious symptoms can be prevented by gradual withdrawal of barbiturates.

101. Isbell, H.: Meeting a growing menace—Drug addiction. *The Merck Report* 60:4–9 (1951).

A general clinical article reviewing the etiology, clinical manifestations, and treatment of opioid and barbiturate addictions. The article was aimed at the general practitioners.

102. Isbell, H.: The treatment of barbiturate addiction. *Postgraduate Medicine* 9:256–258 (1951).

Chronic barbiturate intoxication is a true addiction. Sudden withdrawal of barbiturates, or even sudden reduction in the dosage the patient is accustomed to taking, may be followed by convulsions, a delirium, or both. Careful, gradual reduction in the dosage of barbiturates over a period of 2 to 3 weeks is the best method of withdrawing these drugs from addicted persons. Withdrawal of barbiturates should be followed by a long period of rehabilitative therapy, including psychotherapy when indicated.

103. Isbell, H.: What to know about drug addiction. *GP (General Practitioner)* 4:45–52 (1951).

This is a general clinical article dealing with the clinical manifestations, treatment and prevention of dependence on stimulants, depressants, opiates and opioids, and marihuana.

104. Wikler, A.: Clinical aspects of diagnosis and treatment of addiction. *Bulletin of the Menninger Clinic* 15:157–166 (1951).

1952

105. Fraser, H.F. and Isbell, H.: Actions and addiction liabilities of alpha-acetylmethadols in man. *The Journal of Pharmacology and Experimental Therapeutics* 105:458–465 (1952).

dl-, d- and *l*-Alpha-acetylmethadol possess addiction liability. Single subcutaneous or intravenous doses of *d*-alpha-acetylmethadol in former morphine addicts promptly induced a train of morphinelike effects which disappeared in less than 24 hours. Oral administration of *d*-alpha-acetylmethadol was less efficacious than subcutaneous or intravenous administration. Definite morphinelike effects did not appear for 4 to 6 hours after subcutaneous or intravenous injections of *l*-alpha-acetylmethadol. Once developed, the effects of a single dose persisted for 24 to 72 hours. After oral administration of *l*-alpha-acetylmethadol, morphinelike effects were observed 1 hour after administration and persisted for 48 hours. Due to the long length of action, cumulative toxic effects will appear if doses of *l*-alpha-acetylmethadol are not widely spaced in time.

106. Fraser, H.F. and Isbell, H.: Comparative effects of 20 mg of morphine sulfate on nonaddicts and former morphine addicts. *The Journal of Pharmacology and Experimental Therapeutics* 105:498–502 (1952).

The pupillary size (measured photographically), rectal temperature, pulse and respiratory rates, systolic blood pressure, and the incidence of nausea and vomiting were determined before and at hourly intervals after the subcutaneous administration of 20 mg of morphine sulfate to 20 nonaddicts and 24 former addict males. Similar observations were made after the administration of a placebo to 11 former addict and 10 nonaddict males. Neither nonaddicts nor former addicts reacted in a significant manner to a placebo. Following administration of morphine, nonaddicts showed a greater fall in rectal temperature than former addicts; this difference was statistically significant. After morphine the incidence of vomiting was 35 percent in nonaddicts as compared to 12.5 percent in former addicts. Except for these differences no other evidence of residual tolerance to the effects of morphine was observed in these former addicts.

107. Fraser, H.F., Wikler, A., Eisenman, A.J., and Isbell, H. Use of N-allylnormorphine in treatment of methadone poisoning in man. Report of two cases. *Journal of the American Medical Association* 148:1205–1207 (1952).

A Negro male aged 33, a former heroin addict, volunteered for an experiment in which he received 20 mg methadone intravenously at

8:30 a.m. and again at 1:30 p.m. The latter injection induced nausea and weakness followed by sedation which progressed to deep sleep at 4:30 p.m. At 6 p.m. patient was comatose and respiratory rate was 3/minute. Neither artificial respiration nor 375 mg nikethamide intramuscularly benefited the patient. At 7 p.m. deep tendon, gag and corneal reflexes could not be elicited and respiratory rate was 2/minute. Rectal temperature was 35.8° C, pulse was of good quality and the rate was 75/minute. Patient was given 40 mg N-allylnormorphine intravenously. Four minutes later respiratory rate rose to 10/minute and 23 minutes after injection, rate was 23/minute. Seventy minutes after administration of N-allylnormorphine patient was very drowsy but could be aroused by vigorous stimulation. Shortly afterward he walked with assistance. Recovery was progressive and uneventful. Concurrently, another healthy Negro male received from the same bottle 20 mg methadone intravenously at 8:30 a.m. and again at 1:30 p.m. He showed no unusual response. Case 2 is analogous to case 1 and will be described. These two cases illustrate the cumulative effects of successive, relatively large doses of methadone and the reversal of the resulting respiratory depression and coma by N-allylnormorphine. Since this amount of methadone has been given to more than 125 other postaddicts without significant poisoning, a considerable variation of susceptibility occurs.

108. Hill, H.E., Flanary, H.G., Kornetsky, C.H., and Wikler, A.: Relationship of electrically induced pain to the amperage and the wattage of shock stimuli. *Journal of Clinical Investigation* 31:464–472 (1952).

An apparatus has been described that could be modified for controlling either the delivered wattage or the delivered amperage of electrical stimuli of fixed duration, and which provided a safety device to avoid accidental repetitive shocking. With one exception, the data obtained indicated that the power developed by a particular voltage in a biological circuit of a certain measured resistance does not correspond with the power developed at the same physical resistance by the same voltage. This suggests that a biological circuit is characterized not only by resistance, but by unknown capacitance and inductance. Therefore, delivered wattages calculated on the basis of $P=I^2R$, where R is merely the prestimulation biological resistance, are only "apparent" powers. However, under the conditions of our experiments, such "apparent power" corresponded quite closely to I^2R values calculated on the basis of an equivalent physical circuit. Postaddict subjects judged the intensities of electric shocks delivered by the apparatus. The correspondence of the subject's verbal reports with the amperage and the wattage of stimuli was measured separately, and the differences were statistically evaluated. After a practice series which was followed by the application of four stimuli of standard amperage and wattage, resistances were

reduced by scrubbing with saline paste the surfaces to which the electrodes were applied. Two consecutive power series of nine stimuli each were then administered. In each of these test series, one stimulus was of the standard power and four were higher and four were lower powers than the standard. Due to the decrease in resistance following the scrubbing procedure, the amperages of the test stimuli were considerably higher than those of the practice period. In response to each stimulus, the subject reported whether it was "stronger" or "weaker" than the previously administered standard. It was shown quite conclusively that apparent delivered wattage correlates more highly than amperage with estimation of the intensities of electric shock stimuli. The application of these findings to studies on pain and to other problems is discussed.

109. Hill, H.E., Kornetsky, C.H., Flanary, H.F., and Wikler, A.: The effects of anxiety and morphine on the discrimination of intensities of painful stimuli. *Journal of Clinical Investigation* 31:473–480 (1952).

The effects of subcutaneous injections of 15 mg of morphine on the ability of subjects (postaddicts) to judge the intensity of painful electric shock stimuli were studied under two conditions: (a) under formal conditions, proceeding with the experiment without familiarizing the subjects with the potentially fear-inspiring experimental situation; (b) under informal conditions, preceding the experiment with reassurance, demonstration, and explanation designed to allay the subject's anxiety. In both groups six consecutive series of nine stimuli were delivered in each experiment, and the subjects were required to state whether each stimulus was "stronger" or weaker than a standard stimulus. The strength of each stimulus was controlled on the basis of the power (wattage) value delivered to the subject. During the first three series under formal control conditions, a significantly greater number of test stimuli were judged "stronger" in comparison with the standard stimuli than were actually delivered, and the power (wattage) values of the test stimuli at the points of subjective equality (50-percent point) were reduced significantly by administration of morphine, but were not altered by placebos. Under informal control conditions, verbally reported judgments of test stimuli were extremely accurate and power values of the test stimuli at the points of subjective equality were practically identical with those of the standards. Neither morphine nor placebos had any significant effect on the estimation of the intensities of painful stimuli. Under control conditions during the last three series the accuracy of estimation of the intensities of painful stimuli remained practically unchanged in the "Formal" Group but deteriorated in the "Informal" Group. In both groups morphine tended to reduce the magnitude of error, while placebos had no apparent effect. It is concluded that (a)

under conditions which promote anxiety or fear of pain, subjects tend to overestimate the intensities of painful stimuli; (b) morphine reduces such anxiety; (c) under conditions in which anxiety is largely eliminated, little if any overestimation of the intensities of painful stimuli occurs; (d) morphine does not affect the ability of subjects to accurately estimate the intensities of painful stimuli when anxiety is dissipated; and (e) anxiety, particularly that which is associated with anticipation of pain, is one important variable which must be controlled in experimental investigations of problems related to pain and analgesia.

110. Hill, H.E., Kornetsky, C.H., Flanary, H.G., and Wikler, A.: Studies on anxiety associated with anticipation of pain. I. Effects of morphine. *Archives of Neurology and Psychiatry* 67:612–619 (1952).

In former addicts, hand reaction times to visual stimuli on days without morphine were compared with those after subcutaneous injection of 15 mg of morphine sulfate under the following conditions: (a) the subjects were motivated only by a general knowledge of their performance, and (b) the subjects were penalized by a self-administered brief, but strong, electric shock to one hand immediately after each response, which was slower than the shortest previous median value. The shortest reaction times occurred in nonmorphinized subjects who were not penalized for long reaction times. Morphine alone increased reaction times significantly. Electric-shock penalties to nonmorphinized subjects also increased reaction times significantly. When electric-shock penalties were delivered to morphinized subjects, reaction times were not increased above the level effected by morphine alone during the first 1½ hours after injection of the drug; indeed, in some subjects, reaction times under these conditions were shorter than any of the others. It is concluded that morphine reduces the disruptive effects on performance which are associated with anxiety produced by anticipation of pain.

111. Isbell, H.: What to do with a drug addict. (Special report to the Council on Pharmacy and Chemistry). *Journal of the American Medical Association* 149:1220–1223 (1952).

A general article designed to provide information to physicians on treatment and disposition of drug addicts as understood in 1952. Institutional treatment was thought necessary. Drugs should not be given to an addict for self-administration.

112. Wikler, A.: Clinical and electroencephalographic correlations with special reference to epilepsy. *Journal of the American Medical Association* 149:1365–1368 (1952).

Clinical, physiological, and pharmacologic evidence is presented indicating that wide dissociations may occur between electroencephalographic patterns and changes in sensorium, the state of consciousness, sensation, motor activity, and ideation. It is postulated that the alpha and beta rhythms, and the diffuse changes that may occur in the electroencephalogram in the direction of synchronization or desynchronization, are determined by a specific neuronal system that is, at least in part, independent of neuronal systems that subserve behavior. Hence, changes in the electroencephalogram, particularly those that are diffuse and bilaterally synchronous, can represent only one factor that contributes to the genesis of any clinical entity, including epilepsy.

113. WIKLER, A.: A critical analysis of some current concepts in psychiatry. *Psychosomatic Medicine* 14:10–17 (1952).

Acceptance of a monistic concept of mind and body entails the recognition of a number of implications which, at some points, are in conflict with current usage of certain terms in psychiatry. From a monistic standpoint, the terms "psychic," "organic," "physiologic," "biochemical," etc., denote only different frames of reference which may be used to describe the organism in its environment. One is no more fundamental than any other, and phenomena described in terms of one frame of reference do not cause the phenomena described in any other. Conclusions derived from data in one frame of reference cannot be proved or disproved by comparison with data derived in another frame of reference, since the configuration of variables which these sets of data measure are different in each case and overlap only to variable extents. It is therefore of utmost importance in psychiatric research to go beyond the determination of psychophysiological correlations and to investigate the "common denominators" which account for the correlations. Diagnostic terminology in psychiatry should be purely descriptive, and regardless of the frame of reference in which it is expressed, it should not imply anything regarding etiology. When etiologic factors are known, they may be indicated with an adjective indicating whether such are meaningful or not. It should be recognized that "etiology" is always multiple; temporal relations between contributing factors may be indicated by use of such a term as "detonator" or "precipitating" factor. From the monistic standpoint, treatment in psychiatry must be pragmatic, since the choice of a particular technic bears no relation to the frame of reference in which the condition to be treated is most adequately described. With the application of a multiplicity of technics in many frames of reference to research in psychiatry, new methods of treatment may become available which may be used to alter the organism so that its reactivity to stressful stimuli of any kind will be improved.

114. Wikler, A.: Drug addiction in relation to problems of adolescence. *American Journal of Psychiatry* 109:277–278 (1952).

115. Wikler, A.: Experimental pharmacology and the measurement of the subjective response. *Biometrics* 8:227 (1952).

116. Wikler, A.: Fundamentals of scientific research in psychiatry. *Neuropsychiatry* 2:87–98 (1952).

117. Wikler, A.: Mechanisms of action of drugs that modify personality function. *American Journal of Psychiatry* 108:590–599 (1952).

In this paper, an attempt has been made to examine critically what is known concerning the mechanisms through which drugs modify personality function, in terms of subjective experience, overt performance, and neurophysiology. A study of available data and the techniques by which they have been acquired leads to several important general conclusions: (1) Not only is there a considerable degree of incommensurability between "subjective" and "objective" data, but also between data in either category that are acquired with different techniques. (2) The "organism" can never be separated from its "environment," and the two can be described only in terms of mutual interaction. (3) A "stimulus" cannot be defined in terms of its own properties alone, since its capacity to evoke responses is determined in part by antecedent events, and by particular experimental arrangements. These conclusions can be reconciled with a monistic theory of "mind" and "body." However, it may be questioned whether concepts such as "psyche" and "soma," or their equivalents and derivatives, have not outlived their usefulness, and impede progress in psychiatry more than they foster it. An approach more consistent with the facts, which appears to be more useful in research, is one that may be called "instrumental relativity." Its salient features may be stated as follows. In psychiatry, we are concerned with the prediction and alteration of changes in the organism-environment complex at the symbolic level of functional integration. Such changes may be described in terms of various parameters, such as those of language, performance, physics, and chemistry. Each group of parameters constitutes a "frame of reference" for the measurements that are made. The data so acquired may be "explained" in terms of operational constructs ("properties," "functions," "mechanisms," "theories," "laws") that are peculiar to each frame of reference. However, as the data discussed in this paper indicate, any "mechanism" (or other operational construct) in a given frame of reference can be dissociated from all other "mechanisms" in any other frame of reference, and furthermore, the rates of change of operational constructs may vary considerably in different frames of reference. It follows therefore that perfect correla-

tions can never be made between the data acquired with one technique and those with another, although they may be related. This is true even when, because of semantic confusion, we use the same word to describe different operational constructs—e.g., stimulation, depression, inhibition, facilitation, stress, homeostasis, energy, level of integration, etc. Also, cause-and-effect relationships between successive changes in the organism-environment complex can be inferred with confidence only with respect to such changes as are described in a given frame of reference. The use of terms such as psychosomatic in a cause-effect sense is semantically unjustified and is fraught with serious sources of error. Hence there is little justification for the despair of the neurophysiologist who felt that, as far as "mind" was concerned, the head might just as well be stuffed with cotton wool. Although complete equivalence of what are currently termed "mental" and "material" mechanisms can never be attained, the goal of psychiatric research must be the elucidation of mechanisms, or combinations of mechanisms, in multiple frames of reference at the symbolic level of functional integration, between which correlations can be demonstrated in increasingly high degrees of probability. We must be prepared to adopt new techniques for acquiring data, and to revise our operational constructs, including dynamic formulations and classifications of psychiatric disorders, if by so doing prediction and treatment are facilitated. Such flexibility in research at nonsymbolic levels has been the foundation for progress in other medical fields, and promises also to have great value for psychiatry.

118. Wikler, A.: Opiate Addiction. Psychological and neurophysiological aspects in relation to clinical problems. 72 pp. Springfield: Charles C Thomas, 1952.

119. Wikler, A.: Pharmacologic dissociation of behavior and EEG "sleep patterns" in dogs: Morphine, N-allyl-normorphine and atropine. *Proceedings of the Society for Experimental Biology* 79:261–265 (1952).

In unanesthetized, uncurarized dogs certain doses of morphine, N-allylnormorphine or atropine produce similar changes in the EEG, which are identical with, or resemble closely, the "burst-slow wave" patterns which occur in natural sleep or during pentobarbital anesthesia. The synchronizing mechanisms which regulate the electroencephalograms are distinct from those which regulate the state of consciousness, although frequently, they are functionally interlocked. The significance of these findings is discussed with reference to the possible functions of the spontaneous electrical activity of the cerebral cortex.

120. Wikler, A.: A psychodynamic study of a patient during experi-

mental self-regulated readdiction to morphine. *Psychiatric Quarterly* 26:270–293 (1952).

A psychodynamic study was made of a patient with a previous history of drug addiction, during experimental readdiction to morphine in a controlled environment. Material for interpretation was obtained by observation of his behavior, direct interrogation, recording of spontaneous productions, free associations, and dreams. Subjective experiences following injections of morphine appear to be related to direct gratification of "primary" needs, such as hunger, fear of pain, and sexual (general erotic) urges. The terms "normal" and "euphoria" as used by addicts reflect relative degrees of completeness of such gratifications. When "tolerance" to such effects of morphine develops, such gratifications are diminished, but a new source of gratification becomes available through the concomitant development of "physical dependence," which assumes the character of a "primary" need that can be satisfied only by morphinelike drugs. The use of morphine in our culture may serve also as a means of expressing hostility indirectly, though feelings of guilt may also develop. The suffering attendant upon abrupt withdrawal of morphine may serve the purpose of expiating such guilt. "Secondary" needs are relatively little affected by morphine, except through the gratification of "primary" needs. Hence the "personality pattern" of the addict usually undergoes only quantitative changes as a result of the use of morphine, though legal-economic factors may alter the process. However, strong, "physical dependence" tends to promote regression. While morphine tends to "release" stable (not necessarily "normal") reaction patterns, this effect is more than counter-balanced by reduction toward dependency of motivations. "Repression" is therefore little affected by the use of morphine. This is in marked contrast to the effects of alcohol. Divergence in cultural attitudes toward alcohol and opiate addictions are correlated highly with divergence of cultural attitudes toward the overt expression of aggression. This is discussed with reference to the contrasting effects of alcohol and opiates on individuals. The genesis of morphine addiction and the degree of social productivity which is compatible with active addiction are discussed in relation to the dynamics of personality development, the effects of morphine and prevalent cultural attitudes. The ultimate determinant of the motivation to use morphine repeatedly appears to be the relative intensity of such anxiety as is consequent to the inadequate satisfaction of "primary" needs, through mechanisms which may be "normal" or "neurotic."

121. WIKLER, A.: Reactions of dogs without neocortex during cycles of addiction to morphine and methadone. *Archives of Neurology and Psychiatry* 67:672–684 (1952).

Measurements of body temperature, cardiac and respiratory rates, tooth-pain-reaction thresholds, spontaneous motor activity, and behavioral responses to restraint and to nociceptive stimulation were studied during complete addiction cycles in two chronic decorticated dogs. Supportive data were also obtained in studies during partial addiction cycles in 11 other decorticated dogs. Single doses of morphine or methadone regularly lowered body temperature and cardiac and respiratory rates, elevated tooth-pain-reaction thresholds, and reduced spontaneous circling and "sham-rage" responses. During periods of regular, continuous injection of morphine or methadone, tolerance developed to the effects of these drugs on body temperature, tooth-pain-reaction thresholds, spontaneous circling, and "sham-rage" responses. Methadone (2 mg/kg) substituted readily for morphine (5 mg/kg) when tolerance to the latter had been established. However, tolerance to 5 mg of methadone per kg of body weight four times daily was not developed completely during the periods of addiction employed in these studies. After abrupt withdrawal of either morphine or methadone, stereotyped abstinence syndromes developed, which were characterized by (a) an initial period of increased circling, associated with increased general irritability; (b) a period of quiescence, associated with further increase in irritability and exhibition of yawning, rhinorrhea, and salivation; (c) a period of incessant circling, associated with rise in body temperature, cardiac and respiratory rates, vomiting, maintenance of peculiar postures, gnawing and rooting, marked diminution in irritability, and elevation of tooth-pain-reaction thresholds; (d) gradual subsidence of these changes over a 2-week period, with return to preaddiction levels of measurements and patterns of behavior. During stage *c*, single doses of morphine or methadone reduced elevated physiologic variables, and, concomitantly, they enhanced general irritability. True "physical dependence" can be studied only in animal preparations, such as decorticated or spinal dogs, which are incapable of responding to meaningful stimuli. The present findings indicate that the genesis of "physical dependence" during morphine or methadone addiction is related, at least in part, to nonmeaningful, pharmacologic effects of the drugs in question, and not exclusively to factors of symbolic significance. In intact animals and in man, it would be preferable to substitute "nonpurposive abstinence changes" and "purposive abstinence changes" for the terms "physical dependence" and "psychic dependence," which are now in current use. The demonstration that repeated injections of methadone can produce true "physical dependence" in chronic decorticated dogs, as well as in chronic spinal dogs, supports clinical evidence that the regular use of this drug is associated with addiction liability in man. In the dog, the lip-twitch response to electrical stimulation of a tooth-pulp nerve is integrated subcortically,

and the depressant effects of analgesic agents thereon in the intact animal are due, in part at least, to subcortical actions of these drugs.

122. WIKLER, A.: The relationships between clinical effects of barbiturates and their neurophysiological mechanisms of action. *Federation Proceedings* 11:647–652 (1952).

123. WIKLER, A., PESCOR, M.J., KALBAUGH, E.P., and ANGELUCCI, R.J.: Effects of frontal lobotomy on the morphine abstinence syndrome in man. *Archives of Neurology and Psychiatry* 67:510–521 (1952).

Continuous, regular subcutaneous injections of morphine sulfate in increasing doses up to a stabilization level of 30 to 80 mg four times a day were administered to one habitual narcotic addict with pain in a phantom limb and to three patients with schizophrenia of long standing, whose condition did not improve after standard therapies and for whom frontal lobotomy was indicated for therapeutic reasons. The morphine-abstinence syndromes which followed temporary or permanent abrupt and complete withdrawal of the drug were studied quantitatively immediately after frontal lobotomy and again 7 to 46 days after the operation. In the three schizophrenic patients, these morphine-abstinence syndromes were compared with the results of control "test withdrawals" which were made prior to frontal lobotomy in each case. Individual factors appeared to modify considerably the qualitative and quantitative characteristics of the morphine-abstinence syndrome in different patients, but this syndrome was reproducible to a remarkable degree in any one subject. Variations in the rates of development of tolerance to the effects of increasing doses of morphine, and in the intensities of the morphine-abstinence syndrome did not differ significantly in the schizophrenic patients from those which have been observed in nonpsychotic former addicts. "Physical dependence" is not synonymous with "addiction," since none of the schizophrenic patients exhibited interest in, or craving for, morphine at any time during the study. Temporary recessions of bizarre mannerisms and stereotyped abnormal patterns of behavior were observed in two of the three schizophrenic patients concomitantly with the development of the morphine-abstinence syndrome. This is interpreted as a nonspecific response to "stress," which may also play a role in the therapeutic effects of "organic" treatments in psychiatry. Bilateral frontal lobotomy reduced markedly the "purposive" features of the morphine-abstinence syndrome but did not affect the "nonpurposive" abstinence changes if abrupt withdrawal of morphine was delayed as little as 1 week after operation. When withdrawal of morphine was carried out coincidentally with bilateral frontal lobotomy, the "nonpurposive" changes were definitely attenuated, possibly because of temporary reduction in reactivity of the

autonomic nervous system, due to "diaschisis." Integrity of reciprocal pathways from the thalamus to the superior and lateral areas of the anterior frontal cortex and to the rostral orbital cortex is essential for the mechanisms which subserve the "purposive" components of the morphine-abstinence syndrome, but not for those which subserve its "nonpurposive" components. The functional relation of the anterior frontal lobe to "motivation" is discussed. The reduction in the "purposive" features of the morphine-abstinence syndrome by bilateral frontal lobotomy furnishes no data on which to base inferences regarding the "organicity" or "psychogenicity" of this phenomenon. Other experimental data, however, indicate that the genesis of both the "purposive" and the "nonpurposive" components of this syndrome is related, at least in part, to changes in the organism which are independent of symbolic significance, although theoretically such changes may become "conditioned" to meaningful stimuli, and there is some clinical evidence that this does occur.

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124. Fraser, H.F. and Grider, J.A., Jr.: Treatment of drug addiction. *American Journal of Medicine* 14:571–577 (1953).

The physician should realize that treatment of drug addiction of any type is primarily a psychiatric problem and favorable results cannot be anticipated unless treatment has been continued for several months. Attempts to carry out such therapy in the home or office fail almost invariably. The best method of withdrawing heroin, morphine, or similar drugs from addicted patients involves substitution of methadone or whatever opiate or synthetic analgesic the patient had been using, followed by a reduction of a dosage of methadone for a period of about 10 days. Barbiturates should also be withdrawn very slowly from barbiturate addicts. As in the case of morphine addicts statements of barbiturate addicts regarding daily intake may be very unreliable. Patients showing barbiturate intoxication on admission should not be given additional sedatives until signs of intoxication have become mild. Patients who show signs of mild intoxication on admission such as anxiety, weakness, nausea, and tremor are in danger of developing convulsions and/or psychosis. Such cases should be given 0.2 to 0.5 g of pentobarbital orally or parentally at once. If symptoms are not relieved after 1 hour the dose should be repeated. After mild symptoms of intoxication have been established, the patient should be gradually withdrawn at a rate of not more than 0.1 g of pentobarbital daily. The two serious complications of too abrupt withdrawal of barbiturates are convulsions and psychosis.

These symptoms are very similar to those of too abrupt withdrawal of alcohol. While still hospitalized various rehabilitative procedures should be undertaken and probably a minimum of 120 days of hospitalization for a cure is essential. Prevention of addiction would seem to depend on (1) control of source and supervision of dispensing of addicting drugs, (2) prompt and satisfactory treatment of addicts, and (3) a well-directed mental health and education program.

125. Fraser, H.F. and Isbell, H.: Failure of cortisone and ACTH in treatment of the morphine abstinence syndrome. *Annals of Internal Medicine* 38:234–238 (1953).

In the crossover experiments neither cortisone nor ACTH relieved or modified the quality of the symptoms of abstinence from morphine. The eosinophil counts progressively declined to near zero levels during withdrawal and as soon as morphine was resumed they promptly increased to counts observed in the prewithdrawal period. It is possible that ACTH or cortisone might be of benefit in combating such symptoms from morphine abstinence as anorexia and lethargy when they are present 1 to 3 weeks after narcotics have been discontinued. No experiments of this type were performed, and our results have been interpreted only with respect of the inefficacy of cortisone and ACTH in relieving the acute symptoms of morphine abstinence.

126. Fraser, H.F., Shaver, M.R., Maxwell, E.S., and Isbell, H.: Death due to withdrawal of barbiturates. *Annals of Internal Medicine* 38:1319–1325 (1953).

The clinical course and gross and microscopic pathology of a patient who died during the course of the barbiturate abstinence syndrome is presented.

127. Hill, H.E. and Belleville, R.E.: Effects of chronic barbiturate intoxication on motivation and muscular coordination. *Archives of Neurology and Psychiatry* 70:180–188 (1953).

Ten male patients, addicted to barbiturates upon arrival at the Public Health Service Hospital, Lexington, Ky., who volunteered for the study were maintained on large doses of secobarbital (Seconal) for periods ranging from 35 to 90 days. Reaction times to visual stimuli and quantified measures of muscular coordination were taken (a) during the last week of addiction (intoxication), (b) after abrupt withdrawal of the drug, and (c) after recovery from drug effects. Great loss of coordination was found during intoxication and during the first 8 days of the withdrawal period, with gradual improvement continuing through the remaining 10 days. Reaction time was found to be very greatly impaired during intoxication and early in the withdrawal period; but, unlike

coordination, it showed significant improvement soon after withdrawal and thereafter gradually returned to the control level. Differences in reaction time corresponding to various foreperiods, or delay times, were evaluated as motivational differences; i.e., they were evaluated as differences in ability to develop a "set" or a "readiness to respond." Insensitivity to changes in foreperiods was found during intoxication. Sensitivity increased after withdrawal of the drug and was apparently normal after 3 to 5 months of enforced abstinence. In view of the observed severe muscular incoordination and lack of ability to acquire and maintain readiness to respond, it was concluded that the general behavior of chronic barbiturate users is very severely impaired. They lack the ability to prepare for and react efficiently in performing manipulative tasks. It appears, moreover, that they could not anticipate emergencies and that they would be very unsafe machine operators.

128. Isbell, H.: Drug addiction among adolescents. Conferences at the New York Academy of Medicine, 1951–1952. 320 pp. New York: Blakiston Co., 1953.

129. Isbell, H.: Nalline—A specific narcotic antagonist. Clinical and pharmacological observations. *The Merck Report* 62:23–26 (1953).

Nalline is a specific antagonist for respiratory depression caused by morphine, meperidine, methadone, and related drugs. It is useful in the treatment of poisoning due to opiates, in combating opiate-induced respiratory depression in the newborn, and in diagnosing active addiction to drugs of the morphine series.

130. Isbell, H. and Fraser, H.F.: Actions and addiction liability of dithienylbutenylamines in man. *The Journal of Pharmacology and Experimental Therapeutics* 109:417–421 (1953).

Diethylamino- (No. 4185) and ethylmethylamino-1,1-(2'-thienyl)-1-ene (No. 5145) induce behavior resembling that seen after administration of morphine in former morphine addicts. No. 5145 relieved and suppressed abstinence from morphine. No. 4185 effectively suppressed abstinence from morphine. On withdrawal of the No. 5145 compound after substitution for morphine, a definite morphinelike abstinence syndrome was observed. On withdrawal of No. 5145, after 30 days experimental direct addiction in three patients, a definite abstinence syndrome was observed. N-allylnormorphine precipitated abstinence in patients in whom No. 5145 had been substituted for morphine, as well as in the patients who were directly addicted. The dithienylbutenylamines possess addiction liability similar to that of morphine.

131. Isbell, H. and Fraser, H.F.: Actions and addiction liabilities of

Dromoran derivatives in man. *The Journal of Pharmacology and Experimental Therapeutics* 107:524–530 (1953).

The levorotatory isomers of Dromoran and methyl Dromoran account for all the miotic and respiratory depressant effects of the racemates of these compounds. The dextrorotatory isomers have no significant effects on pupillary size or respiratory minute volume. The effects of l-methyl Dromoran appear sooner and are more intense after oral administration, as compared with subcutaneous administration. l-Dromoran is less effective when administered orally. l-Dromoran and l-methyl Dromoran possess addiction liability of a high order. The addicting potentialities of l-methyl Dromoran exceed those of codeine. d-Dromoran and d-methyl Dromoran are devoid of addiction liability.

132. Isbell, H. and White, W.M.: Clinical characteristics of addictions. *American Journal of Medicine* 14:558–565 (1953).

The clinical signs and symptoms of addiction to opiates, synthetic opioids, barbiturates and other hypnotic drugs, cocaine, central stimulants, and marihuana are described. Addiction to opiates and opioids is characterized by the development of almost complete tolerance and by signs of autonomic and central nervous system hyperactivity on abrupt withdrawal. The condition is self-limited and the acute phase lasts about 7–10 days and is followed by a chronic phase consisting chiefly of insomnia, nervousness, aches, and pains that gradually disappear over the course of 3–6 months. Chronic intoxication with hypnotics is associated initially with signs of drunkenness. A fairly high grade of tolerance develops on abrupt withdrawal. An abstinence syndrome consisting of weakness, insomnia, tremors, convulsions, and a delirium occur. These serious symptoms can be prevented by gradual withdrawal of barbiturates or other hypnotics. Chronic use of cocaine, central stimulants, or marihuana does not cause physical dependence and withdrawal treatment is not required.

133. Wikler, A.: Neurophysiological aspects of the opiate and barbiturate abstinence syndromes. In: Merritt, H.H. and Hare, C.C. (eds.): *Metabolic and Toxic Diseases of the Nervous System,* Vol. 32, pp. 269–286. Baltimore: Williams and Wilkins Co., 1953.

134. Wikler, A.: Recent experimental studies on pain and analgesia. *Neurology* 3:656–660 (1953).

Operational analysis of clinical and experimental methods of evaluating pain and analgesia indicates that discrepancies between the results of different methods of investigation are due, at least in part, to unavoidable differences in the constellation of factors that contribute to the data acquired. Some factors are listed, in terms of demonstrable

correlations, which appear to be significant in the genesis of pain and analgesia. It is suggested that in the search for new methods of relieving pain a multifactorial approach be used, instead of any single method that is now available.

135. Wikler, A.: Treatment of opiate addiction and opiate poisoning. In: *Current Therapy*, pp. 649–650 and 768. Philadelphia: W.B. Saunders (1953). In: *Current Therapy* (1954). In: *Current Therapy* (1955).

136. Wikler, A. and Carter, R.L.: Effects of single doses of N-allylnormorphine on hindlimb reflexes of chronic spinal dogs during cycles of morphine addiction. *The Journal of Pharmacology and Experimental Therapeutics* 109:92–101 (1953).

In chronic spinal dogs, N-allylnormorphine (0.2–100 mg/kg) depressed ipsilateral flexor and crossed extensor reflexes slightly, and antagonized or blocked the depressant effects of morphine (2–100 mg/kg) on the same reflexes. However, the data were insufficient to establish precise dose-effect relationships for the antagonism. In some experiments on chronic spinal dogs, N-allylnormorphine not only antagonized or blocked the depressant effects of single doses of morphine on hindlimb reflexes, but also produced hyperactivity of the latter, with spontaneous "running" movements resembling those which occur in these preparations after abrupt withdrawal of morphine following a period of addiction. During addiction to morphine (0.5–5 mg/kg every 6 hours), N-allylnormorphine regularly precipitated hindlimb and general "abstinence syndromes" in chronic spinal dogs, the intensities of which depended on the dose of N-allylnormorphine, the dose level and duration of morphine addiction, and individual factors. As addiction to a fixed daily dose level of morphine proceeded, a given single dose of N-allylnormorphine precipitated "abstinence" syndromes of increasing degrees of severity, and smaller doses sufficed to precipitate "abstinence" syndromes of severity comparable to those produced by larger doses of N-allylnormorphine earlier in the addiction period. Morphine (5–25 mg/kg) failed to ameliorate the "abstinence syndromes" precipitated by N-allylnormorphine in chronic spinal dogs addicted to morphine, and in some experiments intensified the syndrome. N-allylnormorphine precipitated "abstinence syndromes" in chronic spinal dogs addicted to morphine, before the development of tolerance to morphine could be demonstrated in hindlimb reflexes. After administration of massive single doses of morphine sufficient to overcome tolerance, small doses (e.g., 1 mg/kg) of N-allylnormorphine still precipitated "abstinence syndromes," although these were attenuated. After full recovery of reflexes following withdrawal of morphine, N-allylnormorphine failed to precipitate "abstinence syndromes." At

such times, the effects of N-allylnormorphine were identical with those observed prior to addiction. It is concluded that the processes responsible for physical dependence begin very early during morphine addiction, possibly after a single dose, that they are distinct from those which subserve tolerance, and that they are "masked" by the narcotic actions of morphine. N-allylnormorphine appears to antagonize the narcotic effects of morphine, thereby "unmasking" such physical dependence as has developed. Alternative hypotheses regarding possible mechanisms related to such morphine-N-allylnormorphine interactions are discussed.

137. Wikler, A., Fraser, H.F., and Isbell, H.: N-allylnormorphine: Effects of single doses and precipitation of acute "abstinence syndromes" during addiction to morphine, methadone or heroin in man (post-addicts). *The Journal of Pharmacology and Experimental Therapeutics* 109:8–20 (1953).

In previously unmedicated postaddicts, 5–15 mg of N-allylnormorphine produced relaxation and drowsiness in some subjects and disturbing daydreams or acute visual hallucinations in others. Nausea, giddiness, feelings of instability on standing or walking, and diuresis were observed occasionally. Miosis occurred regularly after 15 mg of N-allylnormorphine and this dose produced slowing of cardiac rate, slight elevation of systolic blood pressure, slight lowering of body temperature, and marked increase in circulating eosinophil counts. After 30–75 mg of N-allylnormorphine, dysphoric effects predominated, and miosis and pseudoptosis occurred regularly. The electroencephalographic effects of N-allylnormorphine appeared to depend on the control pattern and the effects of the drug on affect and state of consciousness. Prior to addiction, N-allylnormorphine antagonized the "euphoric" effects of single doses of morphine, methadone or heroin but precipitated no "abstinence" phenomena. However, clear-cut "abstinence syndromes" were promptly induced by subcutaneous injection of 15 mg of N-allylnormorphine after administration of 15 mg of morphine, 10 mg of methadone or 15 mg of heroin four times daily for as short a period as 2 or 3 days. Such "abstinence syndromes" reached peak intensity about 45 to 60 minutes after injection of N-allylnormorphine and subsided to a large extent during the next hour. As addiction to morphine, methadone, or heroin continued, the same dose of N-allylnormorphine precipitated "abstinence syndromes" of greater intensities, and smaller doses precipitated "abstinence syndromes" of intensities equal to those observed earlier during addiction. N-allylnormorphine failed to precipitate "abstinence syndromes" after evidence of physical dependence disappeared following withdrawal of morphine, methadone, or heroin by rapid reduction. The

"abstinence syndromes" precipitated by N-allylnormorphine during addiction to morphine or heroin resembled closely the changes which ensue after abrupt withdrawal of these agents, except for time course. However, the "abstinence syndrome" precipitated by N-allylnormorphine during addiction to methadone was fully as acute and as intense as that observed during addiction to morphine or heroin, and contrasts sharply with the mild course of the methadone abstinence syndrome in man which follows abrupt withdrawal of this synthetic analgesic. It is inferred that (a) the processes responsible for physical dependence on morphine, methadone, and heroin develop very early during addiction; (b) such changes are masked by certain "narcotic" effects of opiatelike drugs; and (c) N-allylnormorphine antagonizes these "narcotic" effects and thereby "unmasks" physical dependence. N-allylnormorphine appears to be a reliable agent, not only for combating toxic effects of opiates, but also in the rapid diagnosis of addiction to morphine, methadone, or heroin.

138. Wikler, A. and Rasor, R.W.: Psychiatric aspects of drug addiction. *American Journal of Medicine* 14:566–570 (1953).

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139. Fraser, H.F. and Isbell, H.: Abstinence syndrome in dogs after chronic barbiturate medication. *The Journal of Pharmacology and Experimental Therapeutics* 112:261–267 (1954).

Twenty-one dogs were intoxicated chronically with secobarbital or amobarbital for 180 to 195 days. When these barbiturates were withdrawn, the dogs showed mild, or else inconsistent, signs of abstinence. Ten dogs were intoxicated chronically with sodium pentobarbital for 180 to 195 days. On withdrawal, all showed loss of weight, and all except two dogs had tremor. In addition, one dog had two grand mal convulsions, a canine type of delirium and a terminal hyperthermia. Fifteen dogs were intoxicated chronically with sodium barbital for 216 to 339 days. After withdrawal of sodium barbital, a definite abstinence syndrome developed which was characterized by the disappearance of signs of intoxication and the appearance of weakness, tremor, anxiety, rapid loss of weight, convulsions, and a canine type of delirium. It was similar to the barbiturate abstinence syndrome seen in man. The thirteen dogs that survived this experiment were reconditioned and then reintoxicated with sodium barbital for 124 to 225 days, and again a characteristic

abstinence syndrome was precipitated when sodium barbital was withdrawn.

140. Fraser, H.F., Isbell, H., Eisenman, A.J., Wikler, A., and Pescor, F.T.: Chronic barbiturate intoxication. Further studies. *Archives of Internal Medicine* 94:34–41 (1954).

Fourteen men in good general health who were addicted to barbiturates volunteered for an experimental study of chronic barbiturate (secobarbital) intoxication. Barbiturates were administered orally in a dose sufficiently large to maintain continuous moderate to severe intoxication for 32 to 48 days and were then withdrawn abruptly. The clinical manifestations of chronic barbiturism resemble those of chronic alcoholism. After abrupt withdrawal of barbiturates, a definite abstinence syndrome developed. The barbiturate-abstinence syndrome is characterized by the disappearance of signs of intoxication, weakness, tremor, great anxiety, anorexia, nausea and vomiting, rapid loss of weight, fever, difficulty in making cardiovascular adjustments on standing, and convulsions of a grand mal type and/or psychosis which resembles alcoholic delirium tremens. Results of psychological, electroencephalographic, and biochemical studies are reported.

141. Fraser, H.F., Nash, T.L., Van Horn, G.D., and Isbell, H.: Use of miotic effect in evaluating analgesic drugs in man. *Archives Internationales de Pharmacodynamie et de Therapie* (Belgium) 98:443–451 (1954).

A technic for evaluating the miotic effects of opiatelike analgesics is described. The intensity and duration of miotic effects produced by these compounds correlate well with their physical dependence supporting characteristics, the incidence of side reactions, and the intensity of morphinelike euphoria induced. Correlations of miotic effects with clinical analgesia are inconsistent. The method is most useful in evaluating single doses of analgesic drugs when it is employed in conjunction with other procedures.

142. Hill, H.E.: An experimental study of disorganization of speech and manual responses in normal subjects. *Journal of Speech Disorders* 19:295–305 (1954).

Disorganization of behavior was investigated by recording speech and manual responses under threat of penalty. During a pretest situation 30 normal speaking subjects learned to execute three responses simultaneously when certain stimuli appeared. Particular right- and left-hand responses and propositional speech were recorded (1) in a control series, (2) following the application of ambiguous stimuli, and (3) in three experimental series subsequent to a modified light-shock condi-

tioning procedure. Disorganization of behavior was scaled according to criteria established upon the findings of the present study and previous experiments. Disorganization of speech and of the responses of each hand were categorized separately according to a four-point scale (0, 1, 2, 3), 3 representing the greatest disturbance. In general, disorganization of speech and manual responses followed the same course. Although speech requirements were the same for both control and experimental procedures, the introduction of ambiguous stimuli for manual responses produced disorganization of speech behavior. The threat of penalty, produced by means of the interpolated conditioning procedure, resulted in very significant disorganization of speech in all subsequent trials. The significant increase in disorganization which followed the conditioning trials was assumed to accompany unfavorable affective anticipatory reactions (anxiety) which were produced by threat of penalty. Supportive evidence for this statement was found in the experimental design, recordings of muscle action potentials, the form of the curves, and in the presence of an adaptation effect.

143. Hill, H.E., Belleville, R.E., and Wikler, A.: Reduction of pain conditioned anxiety by analgesic doses of morphine in rats. *Proceedings of the Society for Experimental Biology* 86:881–884 (1954).

Rats, maintained at 70 percent of satiation weight, were conditioned to press a bar at a rapid and constant rate in a modified Skinner box. After about 15 days of training when this behavior had been thoroughly established, a method for producing conditioned anxiety was introduced. Shortly after each animal began the daily bar-pressing session a 60-cycle tone, which sounded for 4 minutes, was terminated by the application of a strong electrical shock. After several days of conditioning this procedure produced almost complete cessation of bar pressing during the tone period. In testing the effect of a known analgesic the administration of graded doses of morphine (4–11 mg/kg) produced proportional restoration of the inhibited bar pressing. The reduction or elimination of inhibition by morphine was considered to be a reduction of anxiety associated with anticipation of noxious stimuli. The results parallel in all essential details previous methodological work on man, and strongly suggest that the present procedure may be useful as a technic for the screening of possible analgesic drugs.

144. Isbell, H.: Rapid diagnosis of addiction to morphine. *Journal of the American Medical Association* 154:414 (1954).

This editorial outlines the technique of the use of nalorphine in diagnosis of opiate and opioid addiction by precipitating abstinence in patients physically dependent on those drugs.

145. Isbell, H.: Symptoms following withdrawal of alcohol from chronically intoxicated persons. Joint Expert Committees on Mental Health and Alcohol, United Nations, WHO. Geneva, Switzerland, 1954.

Ten former morphine addict volunteers drank 95 percent ethyl alcohol daily for 6–87 days. Only minor symptoms were observed in four patients following withdrawal of alcohol after 7–35 days of drinking. Withdrawal of alcohol from six patients, who drank for 49–87 days, was followed by a characteristic train of symptoms including tremor, weakness, perspiration, insomnia, anxiety, nausea, vomiting, diarrhea, fever, and elevated blood pressure. Two patients had convulsions, and four had visual and/or auditory hallucinations. Mental status in one patient was difficult to evaluate because of therapeutic large amounts of barbiturates. Three patients were able to drink 16.5 to 19.5 ml of 95 percent alcohol hourly without having significant amounts of alcohol in the blood. Increasing dosage beyond these points resulted in high blood levels. When dosage of alcohol was held constant at level just causing a marked rise in blood alcohol concentration, blood levels gradually fell. Increasing dosage then caused blood level to rise again, after which it never fell. Marked intoxication and a high blood alcohol level were associated with a "slower" electroencephalogram; as drinking continued the amount of "slow" activity decreased even though blood levels were quite high. Following withdrawal of alcohol, the percentage of alpha activity declined suddenly at the 15th hour. Later, paroxysmal activity consisting of random spikes and bursts of high voltage slow waves were observed, regardless of whether the patient had a seizure. Withdrawal of alcohol from chronically intoxicated persons is followed by a characteristic train of symptoms including, in some cases, convulsions and delirium.

146. Wikler, A.: Clinical and electroencephalographic studies on the effects of mescaline, N-allylnormorphine and morphine in man. *Journal of Nervous and Mental Disease* 120:157–175 (1954).

The clinical and electroencephalographic effects of mescaline, N-allylnormorphine and morphine were studied in 35 experiments on 21 subjects with previous histories of narcotic addiction. The clinical effects of mescaline included the production of anxiety, visual hallucinations, illusions, mydriasis, sweating, tachycardia, hyperactivity of tendon reflexes, and tremors. The frequencies of the tremors were between 6 and 8 cycles per second and they appeared at rest and were reduced on voluntary intention movement of the affected part. Concomitantly, the electroencephalograms showed no change, intermittent or continuous replacement of alpha activity by low-voltage fast activity, and/or increase in frequency of the alpha rhythms. Morphine and tetraethylammonium chloride were ineffective in relieving the anxiety produced by mescaline. Intravenous injection of barbiturates abolished anxiety promptly. The

clinical effects of N-allylnormorphine included the production of anxiety, irritability fantasies (daydreams), drowsiness, miosis, pseudoptosis, and occasionally, bradycardia. Concomitantly, the electroencephalograms showed no change, intermittent or continuous replacement of alpha activity by low-voltage fast activity with or without random slow rhythms or increased rhythmic slow activity. Morphine was only mildly effective in relieving the anxiety produced by N-allylnormorphine, while intravenous injection of barbiturates abolished anxiety promptly. Intravenous injection of morphine produced an immediate experience described as a "thrill," which was followed by relaxation and euphoria. Concomitantly, the electroencephalograms showed no change or increase in rhythmic alpha activity with or without slowing of alpha frequencies. The data indicate that the clinical and electroencephalographic effects of these drugs are determined not only by the chemical properties of these agents but also by other factors which are not clearly defined. However, the "personality" of the individual, his past experiences with drugs, and the meaning to him of the experimental situation appear to modify drug effects. In general, and regardless of the nature of the drug administered, shifts in the pattern of the electroencephalogram in the direction of desynchronization occurred in association with anxiety, hallucinations, fantasies, illusions or tremors, and in the direction of synchronization in association with euphoria, relaxation, or drowsiness. However, the converse was not true, since such experiences often occurred without any apparent change in electroencephalographic pattern. Detailed analysis of the clinical and electroencephalographic data, and consideration of what is known concerning the functions of the basal reticular and thalamic diffuse projection systems, suggest the following hypothesis: (1) The alpha rhythm of the "resting" electroencephalogram, and the changes in it in the direction of diffusing desynchronization or diffuse synchronization, reflect the activity of one or more neuron systems which, at least in part, are independent of those which subserve such functions as ideation, mood, level of awareness, motility, and sensation. (2) The functions of the "independent" neuron system (or systems) are related to cortical homeostasis. (3) Desynchronization of the electroencephalogram occurs when the activity of "behavior-related" cortical neuron systems becomes, or threatens to become excessive, and synchronization of the electroencephalogram occurs when the activity of "behavior-related" cortical neuron systems becomes, or threatens to become greatly diminished. (4) Desynchronization of the electroencephalogram may serve to reduce the activity of "behavior-related" neuron systems, while synchronization may facilitate such activity. It is pointed out that the "mechanisms" which subserve the psychologic, neurologic, and electroencephalographic changes produced by drugs can all be separated from each other, though frequently

one or more of them are interlocked. The theoretical significance of this conclusion is discussed briefly.

147. WIKLER, A. and RAYPORT, M.: Lower limb reflexes of a "chronic spinal" man in cycles of morphine and methadone addiction. *Archives of Neurology and Psychiatry* 71:160–170 (1954).

Studies relevant to problems concerning the genesis of the opiate abstinence syndrome were made on a patient with virtually complete residual upper thoracic transverse myelopathy consequent to syphilitic meningomyelitis, who had been addicted to opiates in the past and who volunteered for these experiments. Single doses of morphine sulfate (15 mg) depressed nociceptive flexor reflexes elicited from the skin of the medial aspect of the thigh or leg but had no effect on stretch reflexes. During active addiction to morphine (final dosage level 60 mg four times daily), stretch reflexes became hyperactive, while partial tolerance to the depressive effects of morphine on the flexor reflex developed after an initial period of further depression. On abrupt withdrawal of morphine, stretch reflexes were depressed, while nociceptive flexor reflexes and spontaneous lower limb activity increased markedly. Such "lower limb abstinence phenomena" were promptly abolished by resumption of morphine injections. Methadone, in a ratio of 1 mg of this drug for 3 mg of morphine sulfate, prevented the appearance of lower limb abstinence phenomena. On withdrawal of methadone, lower limb abstinence phenomena appeared, and these persisted with diminishing intensity for about 90 days. Prior to morphine addiction, single doses of nalorphine (Nalline) hydrochloride, 15 mg, exerted actions on spinal cord reflexes that were similar to those of morphine: They depressed nociceptive flexor reflexes and reduced both passive resistance and the severity of mass reflexes in the lower limbs. During morphine addiction, a single dose of nalorphine hydrochloride (6 mg) precipitated acute "abstinence syndromes," both rostral and caudal, to the level of "physiological" transection of the spinal cord that were similar to, but much severer than, those observed after abrupt withdrawal of morphine. The lower limb abstinence syndrome in man which ensues after abrupt withdrawal of morphine or methadone following a period of addiction to either of these agents is similar to that observed in chronic spinal dogs. It is inferred, therefore, that, as in the dog, the genesis of the opiate abstinence syndrome in man is related, at least in part, to physiological changes that occur in the entire neuraxis, including the spinal cord, and that these involve primarily certain internuncial neuron systems that undergo cyclic depression and excitation during opiate addiction. Such excitatory processes increase progressively as addiction continues, and they become manifest on abrupt withdrawal of opiates, or after administration of a single dose of an opiate antagonist, such as nalorphine.

1955

148. Hill, H.E., Belleville, R.E., and Wikler, A.: Studies on anxiety associated with anticipation of pain. II. Comparative effects of pentobarbital and morphine. *Archives of Neurology and Psychiatry.* 73:602–608 (1955).

In 72 subjects who were former drug addicts, repeated self-penalization for slow visuomanual reaction times produced a striking disruption of performance, which was manifested by marked increase in the latency of the responses (slowing of reaction time). Following administration of morphine (15 mg. i. m.) such disruption was greatly reduced, and, furthermore, morphine prevented any significant effect on such shock penalties upon reaction times. In contrast, administration of pentobarbital (250 mg. i. m.) failed to reduce the disruption of performance which accompanies painful self-penalization; indeed, pentobarbital appeared to enhance the effects of shock penalties, although the increase was not statistically significant. It is concluded that, whereas morphine, as previously demonstrated, acts in a powerful manner to relieve anxiety associated with the anticipation of severe pain, this attribute is not shared by pentobarbital. The significance of these findings is discussed with reference to the problems of analgesia.

149. Isbell, H.: Barbiturate poisoning: Chronic barbiturate intoxication (barbiturate addiction). In: Cecil, R.L., and Loeb R.F. (Eds.): *A Textbook of Medicine,* ed. 9, pp. 553–559. Philadelphia: W.B. Saunders, 1955.

150. Isbell, H.: Craving for alcohol. *Quarterly Journal of Studies of Alcohol.* 16:34–64 (1955).

Two kinds of "craving" for alcohol are postulated. The first is a "physical" or nonsymbolic craving which occurs in persons who have been drinking excessive amounts of alcohol for long periods of time, and is manifested by symptoms on withdrawal of alcohol. This type of craving is believed to be due to physiological alterations, the mechanism of which is not yet understood. The chief importance of physical craving is that it tends to make drinking bouts even more protracted and continuous. The second kind (or kinds) of craving is thought to account for initial abuse of alcohol, and for relapse after abstinence. It is postulated that this second kind of craving is chiefly psychological in origin.

151. Isbell, H.: Medical aspects of opiate addiction. *Bulletin of the New York Academy of Medicine.* 31:886–901 (1955).

This paper discusses the etiology, psychology, pharmacology, clinical manifestations, and treatment of opiate and opioid addiction. Legal

control of opiates and opioids remains the most effective method of prevention.

152. Isbell, H.: Opiate addiction: Present status of treatment and research. Report of Council, American Medical Association Committee on Narcotic Addiction, Chicago, 1955.

153. Isbell, H.: Opium poisoning: Cocaine poisoning: Chronic poisoning and sympathomimetic amines. In: Cecil and Loeb (ed.): *A Textbook of Medicine* ed. 9, pp. 570–578. Philadelphia: W. B. Saunders Co., 1955.

154. Isbell, H., Fraser, H.F., Wikler, A., Belleville, R.E., and Eisenman, A.J.: An experimental study of the etiology of "rum fits" and delirium tremens. *Quarterly Journal of Studies of Alcohol.* 16:1–33 (1955).

Ten healthy morphine addicts who had been abstinent from narcotics for at least 3 months volunteered for a study of chronic intoxication with alcohol. The objective was to maintain each subject continually in the maximum state of intoxication compatible with safe ambulatory management for a period of 6 to 13 weeks, and then to discontinue alcohol abruptly. Alcohol was given orally at intervals of 1 or 2 hours from 6 a.m. to 12 midnight, with supplementary drinks at 2 a.m. or 3 a.m., and in an average daily dose of 266 to 489 ml of 95 percent ethyl alcohol for 7 to 87 days. Convulsions and delirium did not appear during the period in which patients were consuming large amounts of alcohol sufficient to maintain high blood alcohol levels. Three patients withdrew from the experiment after 16 days of drinking, or less, and one after 24 days of drinking. The symptoms, consisting of tremulousness, nausea, perspiration, and insomnia, were mild and of brief duration following discontinuance of alcohol by these patients. Six of the patients drank for 48 to 87 days. Following abrupt withdrawal of alcohol, all developed tremors, marked weakness, nausea, vomiting, diarrhea, hyperreflexia, fever, and hypertension. Two of these six patients had seizures; three had a frank delirium (one of these was receiving large amounts of barbiturates at the time delirium occurred); two had transient visual or auditory hallucinations or both; and one escaped both convulsions and hallucinations. These phenomena occurred despite the ingestion of an adequate diet, with multiple vitamin supplements, throughout the periods of intoxication and withdrawal. The intensity of symptoms following withdrawal of alcohol appeared to be correlated roughly with the amount of alcohol consumed and with the length of the period of intoxication. A characteristic electroencephalographic pattern was obtained during chronic intoxication with alcohol and during the withdrawal period. Early during chronic intoxication, the EEG's were

generally slowed whenever the patients had high blood alcohol levels and were showing clinical evidence of intoxication. Later during chronic intoxication, the EEG's were not as slow, even though blood alcohol levels were higher than during the early part of the period of intoxication. Following withdrawal of alcohol, the EEG first became normal. Between the 16th and 33rd hours of abstinence, the percentage of alpha activity declined and random spikes and bursts of slow waves were observed. The concentration of alcohol in blood (usually determined with an automatic breathmeter) was followed in three of the patients. As long as the patients were drinking between 397 and 466 ml of alcohol daily or less, blood alcohol levels were less than 50 mg per 100 ml and clinical evidence of intoxication was not present. Elevation of the alcohol intake to between 430 and 479 ml per day was followed by a rise in blood levels to between 150 and 250 mg per 100 ml, accompanied by evidence of marked intoxication. When the dosage of alcohol which initially caused high blood alcohol levels was maintained, the concentration of alcohol in the blood fell slowly and nearly reached zero. A small increase in the dosage of alcohol and a change in the schedule of drinking was followed by a second elevation in the blood alcohol concentrations. Thereafter blood alcohol levels did not fall until alcohol was withdrawn. No evidence of residual impairment could be detected 3 months after discontinuance of drinking, as judged by physical, psychiatric, psychological, laboratory, and electroenephalographic examinations.

155. McLean, A., Monroe, J.J., Yolles, S., Hill, H.E., and Storrow, H.A.: Acceptability for psychotherapy in institutionalized narcotic addicts. *Archives of Neurology and Psychiatry* 74:356–362 (1955).

The purpose of this investigation was to study the possibility of developing a screening procedure for selecting patients for psychotherapy, to attempt isolation of patient characteristics by which psychiatrists judge acceptability for such therapy, and to obtain an estimate of the percentage of addicts who would be termed acceptable for psychotherapy. Consonant with these purposes, 100 institutionalized addict patients were individually interviewed for 3 hours in an effort to isolate those that would be more acceptable for psychotherapy. To determine personality characteristics and sociological data that would differentiate the acceptable from the less acceptable, a battery of psychological tests, a social service questionnaire, and a detailed psychiatric social service evaluation were completed on each patient. Judgments of acceptability were made by three psychotherapists, who each interviewed approximately one-third of the sample. Acceptability so judged was the criterion with which all other estimates were correlated. Forty-six percent of the sample of narcotic

addicts studied were considered acceptable for psychotherapy. The patients' ability to verbalize feelings, spontaneously produce problems for discussion, and give evidence of original thinking appeared to be significant in placing the patient in the acceptable group. Patients in this group were also more apt to ask for aid with their problems, and showed more evidence of previous ability to modify their patterns of living. Estimates of acceptability made by psychiatric social workers based upon a formal social service questionnaire, as well as on the unstructured hour interview, correlated significantly with the psychotherapists' judgments. Certain psychological measures, including tests of verbal intelligence and degree of manifest anxiety, were significant predictors of acceptability. Finally, various combinations of screening procedures demonstrated that patients judged to be acceptable for therapy by psychiatrists could be selected from a larger group of patients by social service interviews and psychological tests with a high degree of accuracy.

156. Wikler, A.: Rationale of the diagnosis and treatment of addictions. *The Connecticut State Medical Journal* 19:560–568 (1955).

From the standpoint of the clinical problem involved, drug addiction is defined as "pharmacological dependence" (both "psychic" and "physical"), and its diagnosis is based on the demonstration of an abstinence syndrome. Currently, opiates, barbiturates, and alcohol are the most commonly used "addicting" drugs. Other agents, like cocaine, amphetamine, and marihuana may produce dangerous toxic effects when used in excessive amounts, but the clinical problem involved differs from that of addiction, since abrupt withdrawal of such agents produces neither intensified "craving" nor distressing physical disturbances. Treatment of drug addiction may be divided into two phases; withdrawal of drugs and rehabilitation. Withdrawal of opiates can be accomplished most readily by the substitution of methadone by the oral route, and rapid reduction of methadone dosage over a period of 7 to 10 days following a short period of "stabilization." Barbiturates should be withdrawn by gradual reduction, over a period of 3 weeks or more, following a short period of stabilization on pentobarbital. The problem of the management of alcohol withdrawal requires further investigation. The rehabilitation program includes confinement in a drug-free environment for 4 to 6 months, vocational training and occupational therapy, and formal psychotherapy when possible. The rationale of the diagnosis and treatment of drug addiction is discussed from the standpoints both of empirical evidence and of theoretical formulations of the psychological and physiological mechanisms of addiction. Abstinence phenomena are viewed from the standpoint of the "counter-adaptation" theory, and attention is directed to the important role which, among other factors, previous pharmacologic dependence may play in the

genesis of subsequent relapse. Areas for future research, both of a psychological and physiological nature, are indicated in relation to both the "nonpurposive" and "purposive" abstinence phenomena that characterize the clinical problem of drug addiction.

157. Wikler, A., Fraser, H.F., Isbell, H., and Pescor, F.T.: Electroencephalograms during cycles of addiction to barbiturates in man. *Electroencephalography and Clinical Neurophysiology* 7:1–14 (1955).

The clinical and electroencephalographic changes which occur during chronic secobarbital intoxication and after abrupt withdrawal of this drug were studied experimentally in two groups of former narcotic addicts without previous histories of epilepsy or psychosis: group I, consisting of 14 individuals receiving 0.9 to 2.6 g daily in divided doses for 33–89 days, and group II, including 21 individuals receiving 0.6 to 0.8 g of the same drug daily for 38–58 days. During the period of chronic intoxication the subjects in group I displayed varying degrees of ataxia, dysarthria, and other changes resembling those of cerebellar dysfunction, as well as marked changes in affect, sensorium, and judgment. Concomitantly, electroencephalograms were characterized by mixed rhythmic fast and slow abnormalities, mainly in frontal and parietal tracings. Tolerance developed to the clinical effects of barbiturates, but not to the electroencephalographic effects. After abrupt withdrawal of barbiturates, varying degrees of anxiety, tremulousness, postural faintness, anorexia, insomnia, and weight loss developed in almost all the subjects. In addition, 79 percent exhibited one to four generalized convulsions on the second or third day of abstinence, and 65 percent displayed psychoses, generally in the form of agitated delirium, between the fourth and seventh day of abstinence. Concomitantly, marked changes appeared in the majority of electroencephalograms, generally in the direction of periodic hypersynchronization, and with the frequent appearance of mixed spike and slow wave or 4 c/sec "spike-and-dome" paroxysmal discharges. After the eighth day, clinical recovery proceeded uneventfully, and electroencephalograms assumed a normal pattern in the majority of cases, with only mild abnormalities in the remainder. During the period of chronic intoxication, the subjects in group II displayed mild or no evidence of ataxia, etc. Concomitantly, electroencephalograms were characterized by predominance of rhythmic fast activity in the frontal and parietal tracings. After abrupt withdrawal of barbiturates, abstinence phenomena were similar to but much milder than those observed in group I. Only two subjects exhibited seizures, and none developed psychosis. In general, concomitant alterations in the electroencephalograms were similar to but milder than those in group I, with two striking exceptions. In these, paroxysmal discharges were more common than in any record obtained in group I. Clinical recovery

proceeded uneventfully, while electroencephalograms assumed normal patterns in about half of the group, with mild random abnormalities in the remainder. No one-to-one correlations could be demonstrated between any given clinical state and any given electroencephalographic pattern. However, the occurrence of clinical seizures was most commonly associated with random slow, random spike, diffusely slow, or paroxysmal activity in electroencephalograms, and slow abnormalities of various sorts predominated during periods of psychosis. The electroencephalographic changes occurring during cycles of addiction to barbiturates are discussed with reference to possible neurophysiological mechanisms.

1956

158. Belleville, R.E.: MMPI score changes induced by lysergic acid diethylamide (LSD–25). *Journal of Clinical Psychology* 12:279–282 (1956).

This study was undertaken to investigate some of the psychological effects of lysergic acid diethylamide (LSD–25) and to evaluate the MMPI as an instrument for measuring personality changes produced by pharmaceutical agents. Twenty-four former narcotic addicts were given the MMPI under control, placebo, and LSD conditions. Analysis of variance showed significant differences in T-scores between control and LSD conditions and between placebo and LSD conditions on the Pa, Pt, Sc, and A scales. No significant placebo effects were found. The conclusion was drawn that the MMPI is sensitive to some of the major psychologic changes produced by LSD–25, and the suggestion was made that this inventory could find wider use in clinical situations in which drugs are employed.

159. Fraser, H.F. and Isbell, H.: Chlorpromazine and reserpine: (A) Effects of each and of combinations of each with morphine. (B) Failure of each in treatment of abstinence from morphine. *Archives of Neurology and Psychiatry* 76:257–262 (1956).

In nontolerant former opiate addicts, chlorpromazine enhanced the miotic effects of morphine and prolonged some of the subjective effects. One milligram of reserpine given orally and concurrently with 30 mg of morphine subcutaneously did not increase the effects of morphine. In patients addicted to morphine, neither chlorpromazine nor reserpine administered orally or intramuscularly reduced the intensity of abstinence from morphine.

160. Fraser, H.F., Van Horn, G.D., and Isbell, H. Studies on

N-allylnormorphine in man: Antagonism to morphine and heroin and effects of mixtures of N-allylnormorphine and morphine. *American Journal of the Medical Sciences* 231:1–8 (1956).

In former morphine addicts nalorphine (NAM) in doses of 3, 6, and 10 mg subcutaneously caused lowering of body temperature and depression of respiratory minute volume approximately equivalent to the effect of 30 mg of morphine, and only slight pupillary constriction. No significant effects on pulse and respiratory rates or blood pressure occurred. When NAM (3, 6, or 10 mg) was given simultaneously with 30 mg of morphine, or when 10 mg of NAM was given 1¾ hours after 30 mg of morphine, the "euphoric" and miotic effects of the morphine were blocked or diminished. Depression of body temperature and respiration induced by morphine, however, was not antagonized. Ten milligrams of NAM administered simultaneously with 10 mg of heroin antagonized the miotic but not the respiratory-depressant effect of the heroin. NAM was effective orally but a much greater dose was required.

161. Hill, H.E.: Studies on pain and analgesia. *Psychological Record* 6:17–23 (1956).

A brief review of experimental studies of morphine-produced analgesia in man and discussion of the limitations inherent in the study of subjective responses are presented. The importance of changes in affect responses to pain as opposed to changes in perception of painful stimuli in explaining morphine-produced analgesia is hypothesized, and the experimental data supporting that hypothesis are discussed.

162. Isbell, H. Abuse of barbiturates.: *Journal of the American Medical Association.* 162:660 (1956).

Chronic ingestion of 0.8 g of pentobarbital or secobarbital creates a kind of physical dependence manifest by anxiety, weakness, insomnia, tremors, convulsions, and delirium after abrupt withdrawal. Chronic intoxication with and abstinence from barbiturates has similarities to phenomena observed in chronic alcoholism. Physicians should exercise care in prescribing barbiturates.

163. Isbell, H.: Drug addiction (pharmacopsychosis, morphine, or other drug habit; morphinism; cocainism; barbiturism). *Merck Manual* ed. 9, pp. 1337–1343. Rahway, N.J.: Merck and Co., 1956.

164. Isbell, H.: Minimal dosage of barbiturates required to produce physical dependence. *World Health Organization.* APD/75 (1956).

In adult human males, ingestion of 0.4 g or less of secobarbital or pentobarbital daily does not create a clinical detectable degree of physical dependence. "Minor" symptoms of abstinence appeared in abrupt

withdrawal of patients taking 0.6 g of secobarbital or pentobarbital daily. All patients taking 0.8 g daily had minor symptoms, one of five had a convulsion and two of five had hallucinations without clouding of consciousness. Fifteen of 19 patients taking 0.9 or more g daily had convulsions and 12 of 15 had a delirium. Withdrawal treatment is not required in patients taking 0.4 g of pentobarbital or secobarbital daily. The length of time required to produce clinically significant degrees of physical dependence at varying dosages requires further investigation.

165. Isbell, H.: The search for a nonaddicting analgesic. *Journal of the American Medical Association.* 161:1254 (1956).

In general, addiction liability parallels analgesic potency in both derivatives of morphine and in synthetic opioids. The antagonist nalorphine and possibly other antagonists represent the most promising lead for developing a nonaddicting analgesic.

166. Isbell, H.: Studies on the diethylamide of lysergic acid. Development of tolerance and effects of tranquilizing drugs on the reaction. Prize Lecture. Lilly Research Laboratories, Indianapolis, Ind., 15 March 1956.

167. Isbell, H.: Trends in research on opiate addiction. *Transactions and Studies of the College of Physicians of Philadelphia.* 24:1–10 (1956).

Efforts to develop a nonaddicting analgesic drug which have been carried on over the past 25 years have not been successful, unless the opiate antagonist N-allylnormorphine proves to be such an agent. Analgesia and addiction liability have been associated in six distinct chemical families of analgesics. A change in the pharmacological screening methods is needed. Drugs which have any chemical relationship to the presently known classes of analgesics should be shunned and drugs which give typical morphinelike patterns of effect in lower animals should be avoided. Drugs that do not produce morphinelike patterns of effect in lower animals should be studied for possible analgesic effects. The neurophysiological and biochemical approaches to addiction have yielded a great deal of information which permits some understanding of the problems of tolerance and physical dependence. Neurophysiological data on the effects of addiction on levels of the central nervous system between the spinal cord and cerebral cortex are badly needed. Useful data on changes in cellular chemistry during addiction are not available. This latter line of investigation should be pursued. The psychological approach to addiction has yielded information on the personalities of addicts and hypotheses concerning addiction in terms of theories of personality. Attempts are now being made to explain the effects of drugs in terms of more exact psychological and

neurophysiological mechanisms. Better methods of measuring both types of effects are being devised. Great progress in this area can be expected within the next several years. Sociological research has shown that addiction is associated with economic deprivation. Studies of more subtle sociological factors are now being undertaken.

168. Isbell, H., Belleville, R.E., Fraser, H.F., Wikler, A., and Logan, C.R.: Studies on lysergic acid diethylamide (LSD–25). I. Effects in former morphine addicts and development of tolerance during chronic intoxication. *Archives of Neurology and Psychiatry* 76:468–478 (1956).

In former opiate addicts, the diethylamide of lysergic acid (LSD–25) induced anxiety, mood changes, feelings of unreality, visual perceptual distortion, optical hallucinations, depersonalization, and derealization. Concomitantly, resting blood pressure was elevated, pupils were dilated, and the tendon reflexes were accentuated. Characteristics of the LSD reaction appeared to be the same in former opiate addicts and in nonaddicts.

The degree of both the "mental" and the "nonmental" changes increased with the dose of LSD. The intensity of the reaction induced by LSD remained the same when the same dose was repeated after an interval of a week or more. When LSD was given daily, tolerance was evident after administration for only 3 days. After tolerance was well developed, administration of as much as four times the standard dose of LSD did not restore the original intensity of the reaction. On discontinuation of LSD, tolerance was lost as rapidly as it was developed.

169. Wikler, A., Pescor, F.T., Fraser, H.F., and Isbell, H.: Electroencephalographic changes associated with chronic alcoholic intoxication and the alcohol abstinence syndrome. *American Journal of Psychiatry.* 113:106–114 (1956).

Correlative data on EEG changes, behavioral alterations, and variations in blood alcohol level were obtained in three former narcotic addicts without anamnestic, neurological, or EEG evidence of central nervous system disorder, who received averages of 458–489 cm^3 of 95 percent ethyl alcohol daily for 48–55 days followed by abrupt withdrawal of the drug, under controlled experimental conditions. During chronic alcoholic intoxication, blood alcohol levels varied with particular procedures that were carried out, but were maintained for long periods at about 200 mg percent. Initially, EEG's were diffusely slowed, and this change persisted in milder degree during the remainder of the chronic intoxication period. However, EEG evidence of partial, though precarious, "metabolic" and "tissue" tolerance was obtained, which corresponded roughly to variations in degrees of behavioral intoxication. By

the 15th–19th hour of abstinence, blood alcohol levels had fallen to zero. Anxiety, tremulousness, weakness, and profuse perspiration were exhibited by all subjects, and transient, mild but definite dysrhythmias were noted in the EEG. In addition, one subject developed transitory visual hallucinations, and at the 41st hour of abstinence, a generalized seizure. Another developed hyperreflexia, tachycardia, elevation of blood pressure, fever, nausea, vomiting, and diarrhea with transitory hallucinosis during the first 2 days of abstinence, and classical delirium tremens on the 4th day. No specific EEG change could be correlated with such mental changes. All subjects recovered fully within 3 weeks after abrupt withdrawal of alcohol. It is concluded that "rum fits" and delirium tremens can be precipitated by abrupt withdrawal of alcohol in persons continually intoxicated for 48 days or more, that these phenomena may develop in individuals without evidence of preexisting disorder of the central nervous system and that alcohol is an addicting drug in the sense that it can produce pharmacological dependence, both "psychic" and "physical." The clinical and electroencephalographic changes that occur in cycles of addiction to alcohol and barbiturates are compared and contrasted.

170. Wikler, A.: The use of drugs in psychiatric research. *American Journal of Psychiatry* 112:961–969 (1956).

1957

171. Belleville, R.E. and Fraser, H.F.: Tolerance to some effects of barbiturates. *The Journal of Pharmacology and Experimental Therapeutics* 120:469–474 (1957).

Eighteen healthy male postaddicts who volunteered to take barbiturates for 90 days were studied by means of clinical observation and performance on psychomotor tests under control and chronic drug administration conditions, and following withdrawal of drugs. Ten men received 0.4 g of secobarbital daily divided among four equal doses, and eight men received pentobarbital in the same dose schedule. The effects of both drugs were found to be quite similar. No appreciable effects on temperature, blood pressure, pulse, respiratory rate, caloric intake, or body weight were observed during the course of the experiment. Tolerance was demonstrated on all measures showing an initial barbiturate effect, including hours of sleep, intoxication scores, and psychomotor test performance.

172. Essig, C.F. and Ainslie, J.D.: Addiction to meprobamate

(Equanil, Miltown). *Journal of the American Medical Association* 164:1382 (1957).

This paper reports on a male and female patient admitted to the U.S. Public Health Service Hospital, Lexington, Ky., who had been ingesting large doses of meprobamate daily. When the meprobamate was discontinued, convulsions, abnormal electroencephalograms, anxiety, insomnia, nervousness, and headache were observed. In addition, five dogs were experimentally addicted to large doses of meprobamate and following withdrawal restlessness, tremors, violent motor hyperactivity, convulsions, and death were observed. These observations confirm other observations that chronic use of large doses of meprobamate produces physical dependence of the barbiturate type.

173. Essig, C.F. and Carter, W.W.: Convulsions and bizarre behavior in monkeys receiving chlorpromazine. *Proceedings of the Society for Experimental Biology and Medicine* 95:726–729 (1957).

Chronic administration of chlorpromazine in doses ranging between 44 and 77 mg/kg caused major convulsions in four nonepileptic monkeys and induced behavior suggestive of hallucinations in three of the same animals. The possible clinical significance of these findings was discussed.

174. Essig, C.F. and Flanary, H.G.: An activity method of recording generalized convulsions in experimental animals. *Electroencephalography and Clinical Neurophysiology* 9:348 (1957).

175. Fraser, H.F.: Human pharmacology and clinical uses of nalorphine (N-allylnormorphine). *Medical Clinics of North America* 23:393–403 (1957).

Nalorphine per se has a definite pharmacological action, and whether nalorphine acts as an antagonist for morphine depends on a great many factors—doses of each and, most important of all, whether administration of nalorphine has been preceded by one, several, or an addictive dosage schedule of morphine.

Chemical specificity of nalorphinelike antagonism. N-substitution with allyl, methallyl, propyl, isobutyl, or propargyl groups in the morphine and morphinan series produces an active antagonist, provided the parent compound itself is a potent analgesic. For example, *l*-levorphan (*l*-Dromoran) is a potent analgesic, but the *d*-isomer is inactive. Correspondingly, the allyl derivative of *l*-levorphan is an active antagonist; whereas, the *d*-form is completely inactive. As in the case of nalorphine, levallorphan antagonizes respiratory depression produced by the parent compound levorphan, and also respiratory depression induced by morphine and meperidine. No effective antagonists of the methadone

or meperidine series are known. The allyl derivative of levorphan and that of its methyl ether are effective orally for about 12 hours. Morphine antagonism has been described for the allyl derivative of the analgesic p-cyclohexyloxy-α-phenyl-ethylamine. It is effective orally for approximately 24 hours.

Mechanism of action of nalorphine. Two major hypotheses have been offered: First, molecular competition between nalorphine and morphine for a cellular receptor site, as proposed by several investigators and modified by Fraser and coworkers. Another hypothesis, suggested by Wikler and coworkers and by Lasagna, is distinguished from the former in that it is postulated that at least some degree of physical dependence on morphine or other opiates and opioids is a necessary prerequisite for the morphine-antagonistic actions of nalorphine to occur. The therapeutic uses of nalorphine include: (1) specific antagonists for accidental opiate poisoning, (2) to antagonize moderate to severe opiate-type respiratory depression which develops during the course of analgesia, (3) prevention or treatment of respiratory depression in the newborn, (4) diagnosis and treatment of opiate addiction, and (5) analgesia.

176. Fraser, H.F.: Tolerance to and physical dependence on opiates, barbiturates, and alcohol. In: Rytand, D. (ed.): *Annual Review of Medicine*, Vol. 8, pp. 427–440, Palo Alto, Calif.: Annual Reviews, Inc., 1957.

It is generally accepted that chronic administration of opiates or opioids leads to tolerance and physical dependence, with the precipitation of a characteristic abstinence syndrome when they are discontinued abruptly. The preponderance of evidence now indicates that if barbiturates or alcohol are taken under conditions of chronic abuse, tolerance and physical dependence develop, and a characteristic abstinence syndrome (which differs from that of the opiates) develops when alcohol or barbiturates are discontinued abruptly. Since physical dependence is common to all three intoxications, a common and simplified principle of detoxication naturally follows. This consists of gradual withdrawal of the drug of addiction, or of some equivalent substitute, in order to prevent the development of severe symptoms of abstinence.

177. Fraser, H.F. and Isbell, H.: Addiction liability of new analgesics. I. Further studies on *d*-4-dimethylamino-1,2-diphenyl-3-methyl-2-propionoxybutene (*d*-propoxyphene); II. *l*-(2-morpholinoethyl)-4-phenyl-4-carbethoxypiperidine (NIH–7289); III. *l*-2-(2-hydroxy-2-phenethyl)-4-phenyl-4-carbethoxypiperidine (NIH–7292); IV. *l*-3-methoxy-N-phenethylmorphinan (NIH–7362); V. *d*-2,2-diphenyl-3-methyl-4-morpholinobutyrl-pyrrolidine (NIH–7422). *Committee on*

Drug Addiction and Narcotics. Washington, D.C.: National Academy of Sciences, National Research Council, 1957.

Preliminary reports are submitted to the National Research Council on I, II, III, IV, and V above and describe the chemistry of each.

178. Fraser, H.F., Isbell, H., and Van Horn, G.D.: Effects of morphine as compared with a mixture of morphine and diaminophenylthiazole (Daptazole). *Anesthesiology* 18:531–535 (1957).

Single doses and chronic administration of morphine plus saline produced effects identical with those of morphine plus, 2,4-diamino-5-phenylthiazole, hydrobromide (Daptazole). In nontolerant former opiate addicts, the dosage of morphine given alone may be rapidly increased to 500 mg daily within 10 days.

179. Fraser, H.F., Wikler, A., Isbell, H., and Johnson, N.K.: Partial equivalence of chronic alcohol and barbiturate intoxications. *Quarterly Journal of Studies on Alcohol* 18:541–551 (1957).

Ten morphine addicts in good physical health, eight of whom were addicted to barbiturates, volunteered for an experimental study which involved withdrawal of opiates, continuous intoxication with pentobarbital or secobarbital for 22 to 44 days, substitution of alcohol for barbiturates for 14 days and, finally, abrupt withdrawal of alcohol. The clinical symptoms of the intoxications induced by barbiturates and by alcohol were similar, but after substitution of alcohol the EEG pattern changed from that characteristic of barbiturates to that characteristic of alcohol. The "major" symptoms of abstinence due to abrupt withdrawal of barbiturates are convulsions and delirium. The anticipated frequency and severity of these symptoms were reduced significantly by the substitution of alcohol. The incidence and severity of "minor" symptoms of barbiturate abstinence (anxiety, insomnia, tremor, anorexia, vomiting, and weight loss) were reduced. When alcohol was discontinued abruptly after 14 days of substitution, convulsions or delirium or both appeared in three of nine patients who completed the experiment. It is concluded that alcohol is not a complete substitute for barbiturates in patients chronically intoxicated by pentobarbital or secobarbital, but that it is a partial substitute.

180. Hill, H.E.: Book review: How to help the addict. *Contemporary Psychology* 2:113–114 (1957).

181. Hill, H.E., Belleville, R.E., and Wikler, A.: Motivational determinants in modification of behavior by morphine and pentobarbital. *Archives of Neurology and Psychiatry* 77:28–35 (1957).

Since the description of drugs as either "stimulant" or "depressant" did not appear to be sufficient to account for their behavioral effects, it was proposed that motivational factors must be considered as partial determinants of such effects. The present experiment, designed to test this hypothesis, was carried out on 182 former narcotic addicts. Visual-manual reaction times were measured on separate groups of subjects after the administration of 15 mg of morphine sulfate or 250 mg of pentobarbital sodium, and these were compared with the reaction times of other subjects who received no drug on the test day. Each of these measurements was made under four conditions which differed from each other with respect to the incentive (morphine reward) offered for participation in the experiments. The results indicate that changing incentives significantly modifies control reaction time, as well as the effects of morphine or pentobarbital thereon. Thus, in comparison with the control, both drugs acted either as "stimulants" (accelerated reaction time) or as "depressants" (slowed reaction time) or had no effect, depending on the particular incentive conditions under which they were administered. The actions of these drugs, however, were "specific" with respect to each other: The effect of pentobarbital changes from "depressant" to "stimulant" when conditions changed from "Low Incentive" to "High Incentive," while the action of morphine changed from "stimulant" to "depressant" when identical changes in incentive level were made. Viewed from another standpoint, the results indicate that sensitivity to changes in incentives is reduced by morphine and enhanced by pentobarbital. It is postulated that changes in incentive levels, manipulated by the observer, alter performance through effects on specific motivations. Hence, from the data presented, it is inferred that performance, as well as the effects of drugs thereon, is determined in part by the particular motivations that obtain when the measurements are made. The "specificity" of the effects of any particular drug will therefore be apparent only if the motivations involved in the behavior studied are controlled. Furthermore, it is concluded that drugs exert "specific" effects on particular motivations, and that differences in the attractiveness of drugs for different persons may be partly explained on the basis that motivations acceptable to the subject can be enhanced and unacceptable ones suppressed by use of particular chemical agents.

182. Hill, H.E., Pescor, F.T., Belleville, R.E., and Wikler, A.: Use of differential bar-pressing rates of rats for screening analgesic drugs. I. Techniques and effects of morphine. *The Journal of Pharmacology and Experimental Therapeutics* 120:388–397 (1957).

A behavioral "screening" procedure is described for detecting drugs that have potent analgesic actions similar to those of morphine. Measurements of the relationship between bar-pressing rates of rats in a

Skinner box under various conditions imposed by the experimenters constituted the "screen." These measurements included: (a) "operant level" curves, representing the performance of untrained animals without reinforcements of any kind, (b) "time action" curves, representing the performance of animals trained with food reinforcement over a continuous 108-minute period, and (c) "inhibition" curves, representing the inhibition of bar-pressing for food produced by tone-shock conditioning. Under control and placebo conditions the operant level was found to decrease as a function of time, whereas, after 9 mg/kg of morphine the animals operated the bar at a greatly reduced rate. Time action curves showed no significant changes under control or placebo conditions. Morphine (9 mg/kg) caused a significant, early decrease in rate which continued throughout the testing periods. The nearly complete inhibition of bar-pressing that occurred under control and placebo conditions following the pairing of tone and shock was practically eliminated by 9 mg/kg of morphine. This dose produced a marked restoration of previously inhibited performance, as well as "perseveration" or "stereotype" of response. The "restoration" effect was also shown to be proportional to the dose of morphine. Technical problems inherent in the method and the theoretical significance of the results are discussed. While the pattern of morphine actions on the measures used supports the inference that morphine reduces pain-conditioned "anxiety," this explanation does not appear sufficient to account for the "stereotypy" of performance which was observed. Some areas for further investigation are suggested.

183. Isbell, H. and Logan, C.R.: Studies on the diethylamide of lysergic acid (LSD–25). II. Effects of chlorpromazine, azacyclonol, and reserpine on the intensity of the LSD-reaction. *Archives of Neurology and Psychiatry* 77:350–358 (1957).

Chlorpromazine ameliorates partially the abnormal mental state induced by the diethylamide of lysergic acid (LSD–25) in man. Chlorpromazine has this effect when administered before or after LSD. Azacyclonol (Frenquel) does not reduce the intensity of the LSD psychosis in man. Reserpine does not mitigate the LSD psychosis in man. Patients receiving a combination of reserpine and LSD have severer symptoms than when receiving either drug alone.

184. Wikler, A.: *The relation of psychiatry to pharmacology.* 322 pp. Baltimore: Williams and Wilkins, 1957.

This study of the effects of drugs used in psychiatry in the treatment or investigation of the functional behavioral disorders is based on a survey of the literature during the period 1930 to 1955. It is the first general compilation and summary of this important subject. Drugs

reviewed at length are insulin, carbon dioxide, barbiturates and other anesthetics, amphetamine and methamphetamine, pipradrol, chlorpromazine, reserpine, meprobamate, azacyclonol, *d*-lysergic acid diethylamide, and mescaline, Epinephrine, norepinephrine, acetylcholine and methacholine, pituitary adrenal hormones, and other potent analgesics are considered in relationship to the other drugs. Taking the position of an "experimental psychiatrist" rather than a "pure pharmacologist," the author arranges his material in two sections: "The Effects of Drugs on Human Behavior" (how drugs have been used and what effects have been observed under clinical conditions) and "Theories and Mechanisms of Drug Action" (the correlation of changes drugs produce in human behavior with changes such agents effect in cerebral metabolism, neural organization, and environmental adaptation). This book is an important step toward improved communication between the psychiatrist and the pharmacologist and the recognition that drugs can be used as tools to detect and manipulate variables relevant to the determination of human behavior, normal or abnormal.

1958

185. Eisenman, A.J., Fraser, H.F., Sloan, J.W., and Isbell, H.: Urinary 17-ketosteroid excretion during a cycle of addiction to morphine. *The Journal of Pharmacology and Experimental Therapeutics* 124:305–311 (1958).

Single doses of 45 or more mg of morphine sulfate administered to human male subjects were followed by decreased excretion of 17–KS. Addiction to morphine, lasting from 35 to 144 days, caused a significant fall in the excretion of 17–KS. Evidence of partial tolerance to the depressant effect of morphine on urinary 17–KS appeared during periods of addiction lasting 143 days. A striking rise in urinary 17–KS, with levels usually exceeding those of the predrug period, occurred on the second to fourth day of withdrawal. The maximal increase coincided with the most severe symptoms of abstinence and the greatest drop in eosinophil counts. During recovery, urinary 17–KS returned to preaddiction levels. Administration of ACTH (10 IU) resulted in a striking rise in 17–KS excretion and a fall in eosinophil counts during control, addiction, and recovery periods. Similar responses to 5 and 2½ units occurred. Administration of 5,000 units of chorionic gonadotropin over a 5-day period caused enhanced excretion of 17–KS which was greater during addiction than during control and recovery periods. During addiction there was some evidence of delay in the response to hormonal stimulation. The maximal fall in eosinophil counts was sometimes re-

tarded for about 2 hours after ACTH infusion. The maximal response to gonadotropin was usually postponed for 2 or more days. ACTH and gonadotropin administered in combination did not have additive effects on excretion of urinary 17–KS. A cycle of morphine addiction did not affect the content of butanol-extractable iodine in blood serum.

186. Essig, C.F.: Withdrawal convulsions in dogs following chronic meprobamate intoxication. *Archives of Neurology and Psychiatry* 80:414–417 (1958).

Meprobamate was administered in a high dosage for 124 to 188 days to four dogs. Abrupt withdrawal of the drug was followed by repeated convulsions and death in three dogs and in an induced convulsion in a fourth dog. Meprobamate possesses addiction liabilities and should be prescribed with the same precautions used with barbiturates.

187. Essig, C.F., and Fraser, H.F.: Electroencephalographic changes in man during use and withdrawal of barbiturates in moderate dosage. *Electroencephalography and Clinical Neurophysiology* 10:649–656 (1958).

In contrast to doses of over 0.6 g per day, the withdrawal of 0.4 g daily of secobarbital or pentobarbital after 3 months was not followed by psychotic or convulsive manifestations in any of 18 nonepileptic subjects. Seven of 13 individuals demonstrated some evidence of EEG tolerance to 0.4 g daily of secobarbital or pentobarbital during 90 days. During withdrawal from this same barbiturate regimen, 5 of 18 subjects developed paroxysmal EEG discharges which later disappeared and were not associated with observable clinical abnormalities.

188. Fraser, H.F.: Problems resulting from the use of habituating drugs in industry. I. Pharmacology of habituating drugs. *American Journal of Public Health* 48:561–570 (1958).

Habituating drugs which impair performance and induce physical dependence provoke the most problems in industry and in the general practice of medicine. The most universal offenders in these respects are alcohol and barbiturates. Opiate-type drugs induce physical dependence, of course, but their abuse does not affect as many individuals. Other drugs which induce physical dependence under conditions of abuse are meprobamate and Doriden. Habituating drugs which do not provoke physical dependence include cocaine, marihuana, and the amphetamines. While drugs in this category may produce deleterious effects, their abuse is usually restricted to more isolated segments of the population.

189. Fraser, H.F. and Isbell, H.: Human pharmacology and addiction liability of certain compounds related to morphine or codeine.

Committee on Drug Addiction and Narcotics. Washington, D.C.: National Academy of Sciences, National Research Council, 1958.

190. Fraser, H.F. and Isbell, H.: Progress report. NIMH Addiction Research Center, PHS Hospital, Lexington, Ky. *Committee on Drug Addiction and Narcotics.* Washington D.C.: National Academy of Sciences, National Research Council, 1958.

(-) 3-Hydroxy morphinan HBr (NIH–7539) is the *nor* compound in the morphinan series and corresponds to normorphine in the morphine series. NIH–7539 was tested in single doses using 23 postaddicts in a dose range of 1 to 100 mg. Seventy to 100 mg were less potent than 20 mg of morphine and it induced only slight to moderate miosis. It was substituted in 10 patients stabilized on an average of 230 mg of morphine daily in a dose of 360 mg of NIH–7539 daily. Substitution was incomplete but overall subjectively satisfactory. A direct addiction test was carried out in one patient. The patient was started on 75 mg divided among three subcutaneous doses daily and the dosage gradually increased until he received a total of 120 mg daily on the 17th day. Consecutive doses of NIH-7539 appeared to produce cumulative sedative effects such as those observed in the case of normorphine. As the experiment advanced, gradual but progressive tolerance to the sedative effect was observed. When the drug was discontinued, on the 17th day, a mild but definite abstinence syndrome developed which resembled the abstinence from normorphine. Thus, the parent and the normetabolite of 1-3-hydroxy-morphinan resemble morphine and normorphine respectively.

191. Fraser, H.F., Wikler, A., Essig, C.F., and Isbell, H.: Degree of physical dependence induced by secobarbital or pentobarbital. *Journal of the American Medical Association* 166:126–129 (1958).

Withdrawal symptoms were studied in 50 volunteer subjects who took secobarbital and 11 who took pentobarbital. The drugs were given by mouth, over periods ranging from 32 to 365 days, at several dosage levels and 18 of the subjects received the largest daily dose of 0.9 to 2.2 g daily) compatible with safe ambulatory management. The symptoms following abrupt withdrawal were insignificant in the patients on minimal dosage but severe in those on maximal dosage; convulsions were seen in 14 instances and delirium in 12. A significant degree of physical dependence can be observed in patients receiving these two drugs, but withdrawal symptoms differ from those that follow withdrawal of opiates and they can be avoided by keeping the dosage below 0.4 g per day.

192. Fraser, H.F., Wikler, A., Van Horn, G.D., Eisenman, A.J., and

ISBELL, H.: Human pharmacology and addiction liability of normorphine. *The Journal of Pharmacology and Experimental Therapeutics* 122:359–369 (1958).

In single doses, normorphine caused less sedation, less depression of temperature, less respiratory depression, and less pupillary constriction than did equal doses of morphine. Administration of 9 to 10 mg of normorphine every 6 hours for seven doses caused less, but longer lasting, pupillary constriction than did equal doses of morphine. Cumulation of the sedative effects of normorphine occurred in this experiment. When substituted for morphine in addicted patients, normorphine completely suppressed the morphine abstinence syndrome. The intensity of abstinence observed after withdrawal of normorphine was far less than the intensity of abstinence from morphine. Marked cumulation of sedative effects occurred during direct addiction to normorphine and prevented elevation of the dosage to the level which could easily have been attained with morphine. Partial tolerance to the sedative effects developed. Nalorphine precipitated definite abstinence syndromes in patients addicted to normorphine. Intensity of abstinence after withdrawal of normorphine was slow in onset and milder in degree than abstinence from morphine, methadone, or codeine. As compared with predrug control values, the urinary excretion of 17-hydroxycorticosteriods was depressed during chronic administration of normorphine and elevated transiently after normorphine was discontinued.

193. MONROE, J.J. and HILL, H.E.: The Hill-Monroe Inventory for predicting acceptability for psychotherapy in the institutionalized narcotic addict. *Journal of Clinical Psychology* 14:31–36 (1958).

A questionnaire of 46 items was constructed out of a pool of 180 items for selecting individuals among a drug-addict population who were most acceptable for psychotherapy. The criterion of acceptability was the judgment of psychiatrists made during three 1-hour interviews with each patient. The first study utilized 100 institutionalized narcotic addicts after withdrawal treatment had been completed. An item count was made to find the items which were significantly related to the criterion. Cross validation demonstrated that combinations of items from the questionnaire were 74 percent efficient in predicting psychiatric judgments of acceptability for psychotherapy. For purposes of further refinement, 78 items that differentiated between the more acceptable and the less acceptable patients in the initial study were reduced to 46 by selecting only those empirically valid items which two senior psychiatrists, neither of whom had participated in the original cross-validation, independently judged to reflect the responses of acceptable therapeutic candidates. Normative data for the inventory on 400 sub-

jects were obtained. Validity generalization tests of the predictive efficiency of the 46 item scale were then made on a group of 136 subjects, some of whom had been independently chosen to receive psychotherapy, and some of whom had not been so chosen. When the scale was used with this sample to label those patients scoring more than one standard deviation above the population mean as "acceptable for therapy" most were those for whom psychotherapy had been prescribed.

194. Wikler, A.: Methodology of research in psychological pharmacodynamics. In: *Progress in Psychotherapy* pp. 212–218. New York City: Grune and Stratton, 1958.

Alternative "rationales" for the use of drugs in "psychoexploration" and psychotherapy are discussed. Clinical evidence is reviewed indicating that, rather than revealing the "true personality structure" through "stripping of defenses," drugs modify in specific ways the responses of the subject to the therapist's manipulations, although "personality factors" play an important role in determining the patterns of such drug effects. Experimental evidence for "pattern-specificity" in the behavioral effects of drugs (morphine and pentobarbital) is reviewed. From the data cited, and theoretical considerations, it is inferred that drugs alter "motivations" in specific ways, thus accounting, in part, for variations in the behavioral effects of a given drug in different individuals under the same experimental conditions, and in the same individual under different conditions, as well as for the "pattern-specificities" of different drugs. The problem of "isolating" particular "motivations" for pharmacological studies in man and the advantages and limitations of animal research are discussed. It is concluded that although animal studies can furnish "models" for use in human investigations, the latter are more likely to furnish the definitive data needed for construction of a rationale for the use of drugs in "psychoexploration" and psychotherapy. The scopes and limitations of biochemical, neurophysiologic, and psychological pharmacodynamics are pointed out, and the need for complementary information from these disciplines for adequate understanding of the behavioral effects of drugs in man is stressed.

195. Wikler, A.: Opiates and opiate antagonists. A review of their mechanisms of action in relation to clinical problems. Public Health Monograph #52. Washington, D.C., U.S. Government Printing Office, 1958.

Some recent advances in our knowledge of the mechanisms of action of narcotics have been discussed in connection with (a) the use of "specific" opiate antagonists in the treatment of opiate and

opioid poisoning, as well as in the diagnosis of narcotic "addiction"; (b) analgesia; and (c) problems of drug abuse. Analysis of dose-effect relationships suggests strongly that nalorphine, levallorphan, and their congeners exert their specific antagonistic actions against the depressive effects of narcotics by (a) "molecular competition" at cellular (neuronal) receptor sites and (b) "unmasking" by the antagonists, of the processes responsible for the opiate and opioid "abstinence" syndromes, which may develop as a consequence of the administration of a single massive or of repeated smaller doses of narcotic drugs. The neurophysiological mechanisms through which morphine produces analgesia have been analyzed mainly from the standpoint of the actions of this drug upon central processes involved in some animal "analgesic screening" procedures that have proved to be of great empirical value. Although there are some difficulties in reconciling all of the available data, it appears that the effects of morphine upon these "analgesic-tests" reflexes are exerted through selective depressant actions on interneurons in the spinal cord, coupled, perhaps, with augmentation of supraspinal (cortical and brain stem) inhibition. In addition, morphine appears also to exert selective depressant actions on interneurons in the medulla, in the ascending reticular and certain of the thalamic diffusely projecting systems, in the thalamic relay nuclei, and in the cerebral cortex—actions which may contribute to the genesis of the specific pattern of behavioral change that constitutes morphine analgesia. The psychological mechanisms involved in morphine analgesia have been analyzed mainly from the standpoint of experimental data indicating that one of the major actions of the drug is to reduce "anxiety associated with the anticipation of pain." Problems of "drug abuse" have been analyzed from the standpoint of the hypothesis that relapse after cure (habituation) is mainly a consequence of reinforcement of drug-seeking behavior due, initially, to reduction by the drug of "tensions" arising out of interactions between the personality of the user and his social milieu, and later, of tensions engendered by the development of pharmacogenic dependence (addiction). The intoxicating (euphoric) effects of single doses of opiates in nontolerant individuals have been considered chiefly in relation to the neurophysiological and psychological mechanisms involved in morphine analgesia, on the assumption that these contribute also to the genesis of at least the "negative" type of morphine euphoria. From the neurophysiological standpoint, the basic mechanisms involved in pharmacogenic dependence (both "psychic" and "physical") appear to operate at the cellular (neuronal) level throughout the neuraxis; ablations and transections of portions of the central nervous system may alter the form of the abstinence syndrome, but they do not eliminate it. In addition to the somatic and autonomic systems, the pituitary-adrenal system is also involved in the processes of tolerance and pharmacogenic

dependence. From the psychological standpoint, the rewarding aspects of pharmacogenic dependence are stressed, particularly with reference to alterations of motivation and the enhancement of goal-directed activity that are consequent to the establishment of this state, and with reference to secondary reinforcements derived from alterations in the user's relationships to his social milieu. "Conditioning" theories that have been advanced to account for relapse after cure are discussed, and some recent experimental data supporting such theories are reviewed. While practically no information is available on the neurophysiological mechanisms involved in relapse, possibilities for future research are suggested by a recent report indicating that this phenomenon, which has hitherto defied experimental investigation, can be reproduced in animals.

196. Wikler, A.: Some problems in "experimental psychiatry." *Psychiatric Research Reports,* American Psychiatric Association 9:89–111 (1958).

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197. Eddy, N.B. and Isbell, H.: Addiction liability and narcotics control. *Public Health Reports* 74:755–763 (1959).

The status of United States and international narcotic laws is reviewed. U.S. laws are not sufficiently flexible to permit rational legal classifications of different drugs based on the degree of danger to public health. Distinction between natural opiates and synthetic opioids should be removed and exempt preparations of synthetics permitted. The essential feature of addiction is psychic dependence. Cocaine and marihuana do not produce physical dependence but carry a high degree of risk to public health and so are rigidly controlled by narcotic laws. Amphetamines and other central stimulants can be drugs of dependence but control as rigid as narcotic controls is not desirable. Barbiturates and other central depressants can create both psychic and physical dependence but control as rigid as narcotic controls should not be imposed because of the widespread clinical use of the compounds.

198. Essig, C.F.: Book Review: The barbiturate withdrawal syndrome. A clinical and electroencephalographic study. Wulff, M.H. Thesis, M.D., University of Copenhagen. Issued simultaneously as Electroencephalography and Clinical Neurophysiology. Suppl. 14, 1959. *Journal of the American Medical Association* 171:260–261 (1959).

199. Essig, C.F. and Flanary, H.G.: Convulsions in cats following withdrawal of barbital sodium. *Experimental Neurology* 1:529–533 (1959).

Twenty cats which survived chronic barbital sodium intoxication were withdrawn from the drug to determine whether this species develops abstinence convulsions and, if so, what drug regimen is necessary for their occurrence. Increasing dosages were administered orally for periods ranging from 23 to 217 days so that final dose levels varying from 61 to 279 mg per kilogram were attained. Abrupt withdrawal resulted in generalized convulsions in 11 animals. Ten of these cats had attained final dosage exceeding 173 mg per kilogram. This factor affects the reproducibility of the phenomenon more than duration of intoxication or total amount of drug received.

200. Fraser, H.F. and Isbell, H.: Addiction liabilities of *dl*-2′-hydroxy-5,9-dimethyl-2-(2-phenethyl)-6,7-benzmorphan HBr (NIH-7519) and *l*-3-hydroxy-N-phenacylmorphinan methane sulfonate (NIH-7525). *Committee on Drug Addiction and Narcotics.* Washington, D.C.: National Academy of Sciences, National Research Council, 1959.

The addictiveness of *dl*-2′-hydroxy-5,9-dimethyl-2-(2-phenethyl)-6,7-benzmorphan HBr (NIH–7519) and *l*-3-hydroxy-N-phenacylmorphinan methane sulfonate (NIH–7525) has been evaluated in man. In single doses both NIH–7519 and NIH–7525 are more potent in inducing subjective effects ("euphoria") and in constricting the pupils than is morphine. Both NIH–7519 and NIH–7525 are potent suppressors of abstinence from morphine and are completely adequate substitutes for morphine in addicted persons. Following withdrawal of NIH–7519 and NIH–7525 after substitution for morphine or after direct addiction, definite morphinelike abstinence appeared which tended to be less severe than abstinence following withdrawal of equivalent amounts of morphine.

201. Fraser, H.F. and Isbell, H.: Addictiveness of trifluoperazine (SKF–5019). *Committee on Drug Addiction and Narcotics.* Washington, D.C.: National Academy of Sciences, National Research Council, 1959.

This compound, which chemically is 10-3-(l-methyl-4-piperazinyl)-propyl-2-trifluoromethylphenothiazine dihydrochloride, is a congener of chlorpromazine. In animals it has been reported to possess a spectrum of pharmacological activity resembling that of the parent compound, and in addition, was reported to possess significant "analgesic" activity in lower animals. Since it was possible that this phenothiazine derivative might possess analgesic properties in man, and yet have low or no addictiveness, preliminary screening studies were carried out at the Addiction Research Center.

Effect of Single Doses.—Five nontolerant former morphine addicts, all adult Negro male prisoner volunteers, received either 3 or 5 mg of

SKF–5019 subcutaneously. Pupillary constriction, sedation, and drowsiness were observed in all patients. No patient, however, made a positive identification of the subjective sensations as resembling those of an opiate. Two of three patients who received 5 mg of the compound developed marked twitching and muscular spasm (Parkinsonian equivalent?). In one patient the muscular spasm was so severe that the patient was bent double.

Suppression of Abstinence.—This was evaluated in five patients stabilized on 240 mg of morphine sulfate daily. They received 6 to 16 mg of SKF–5019 in divided doses during a 24-hour period of substitution for morphine. The Himmelsbach hourly point scores following substitution of SKF–5019 were not significantly different from those observed after substitution of saline. Two of the five patients refused to take the third dose of SKF–5019, and all five reported unpleasant symptoms after the drug.

Conclusion.—SKF–5019 possesses no or very low addictiveness of the morphine type.

202. Haertzen, C.A. and Hill, H.E.: Effects of morphine and pentobarbital on differential MMPI profiles. *Journal of Clinical Psychology* 15:434–437 (1959).

The MMPI was given in balanced order to 55 postaddict subjects under control, morphine (60 mg), and pentobarbital (200 mg). Drug effects were assessed for the total group as well as for four subgroups: Primary psychopath (N=12); Neurotic psychopath (N=12); Schizoid psychopath (N=12); and Unclassifiable (N=19). The drugs did not alter scale elevations for the combined group; significant drug effects were dependent upon differential personality characteristics as measured by the MMPI. The only significant change under pentobarbital was a decrease in the Internalization Ratio in the Schizoid and Neurotic groups. Morphine produced unpredicted increases in Hs, Pa, Pt, Sc, and in the Internalization Ratio in the Primary psychopath group, and produced decreases in D, the Anxiety Index, and Internalization Ratio in the Neurotic psychopath. The latter changes were anticipated since it had been hypothesized that one important aspect in the development of addiction to opiates is initial reduction of discomfort, anxiety, and depression in those addicts who show neurotic tendencies. Although the results suggest that opiates reduce sensitivity to interpersonal relations in the Primary psychopath, the implications of the findings for addiction liability of the opiates in this type of individual are not as yet clearly defined.

203. Isbell, H.: Addiction to hypnotic and sedative drugs. *Association of Food and Drug Officials of the United States* 23:35–43 (1959).

Chronic ingestion of barbiturates in high amounts produces a type

of physical dependence different from that caused by morphine and which is manifest by the appearance of weakness, tremors, convulsions, and delirium on abrupt withdrawal. The barbiturate abstinence syndrome is somewhat similar to alcoholic delirium tremens. Similar addiction has been reported after chronic ingestion of paraldehyde, chloral, meprobamate, and glutethimide. Physical dependence on barbiturates is more dangerous to life than physical dependence on opiates. Gradual reduction of barbiturates effectively prevents the serious symptoms seen after abrupt withdrawal.

204. Isbell, H.: Barbiturate poisoning, chronic barbiturate intoxication; opium poisoning; cocaine poisoning; and chronic amphetamine poisoning. In: Cecil, R.L., and Loeb, R.F. (eds.): *A Textbook of Medicine* (ed. 10). pp. 1631–1645. Philadelphia: W.B. Saunders, 1959.

205. Isbell, H.: Comparison of the reactions induced by psilocybin and LSD–25 in man. *Psychopharmacologia* 1:29–38 (1959).

The reaction induced by oral administration of 57 to 114 μg/kg of O-phosphoryl-4-hydroxy-N-dimethyltryptamine (psilocybin) has been compared with that induced by a placebo and LSD–25 (1.0 to 1.5 μg/kg) in nine subjects. Both LSD and psilocybin caused elevations in body temperature, pulse and respiratory rates, and systolic blood pressure. Threshold for elicitation of the knee jerk was decreased by both drugs. After both drugs, abnormal mental states characterized by feelings of strangeness, difficulty in thinking, anxiety, altered sensory perception (particularly visual), elementary and true visual hallucinations, and alterations of body image were reported by the subjects. The effects of psilocybin did not persist as long as those of LSD. LSD is 100 to 150 times as potent as psilocybin.

206. Isbell, H.: Effects of various drugs on the LSD reaction. In: *Psychopharmacology Frontiers*, pp. 362–364. Boston: Little, Brown and Co., 1959.

Chlorpromazine significantly reduced the intensity of the LSD reaction in man. Reserpine had no blocking effect and may have made the LSD response. Azacyclonol, scopolamine, amphetamine, and l-benzyl-2-methyl-5-methoxy-tryptamine (BAS) had no effect. 2-Brom-lysergic acid (BOL) did not block the LSD reaction when administered at the same time as the LSD. Pretreatment with BOL for 3 days prior to administration of LSD did attenuate the LSD reaction probably because of tolerance to BOL and cross-tolerance between BOL and LSD.

207. Isbell, H.: Medical and legal problems involved in narcotic addiction. In: *Proceedings Medicolegal Symposiums.* pp. 19–26. Chicago: American Medical Association, 1959.

This paper was one of several presented at the medicolegal symposium sponsored by the American Medical Association. Evaluation of the results of the clinics that dispensed opiates to addicts around 1920 is impossible because of poor and insufficient data. There are many reasons why such clinics are likely to be unsuccessful. The American Medical Association did not support establishment of clinics. It did support institutional treatment, development of strong postinstitutional care programs, and elimination of criminal penalties for simple possession of narcotics.

208. Isbell, H.: Preliminary clinical assessment of drugs used in mental illness. In: Cole, J.O. and Gerard, R.W. (ed): *Psychopharmacology, Problems in Evaluation*. pp. 317–330. Washington, D.C.: National Academy of Sciences, Pub. No. 583 (1959).

This paper discusses the techniques of preliminary clinical screening (phase I and phase II testing) of psychoactive drugs in human subjects including precautions to be taken.

209. Isbell, H., Logan, C.R., and Miner, E.J.: Studies on lysergic acid diethylamide (LSD–25). II. Attempts to attenuate the LSD-reaction in man by pretreatment with neurohumoral blocking agents. *Archives of Neurological Psychiatry* 81:20–27 (1959).

Pretreatment with the neurohumoral blocking drugs phenoxybenzamine (Dibenzyline), scopolamine, and l-benzyl-2-methyl-5-methoxytryptamine (BAS) did not attenuate or accentuate the lysergic acid diethylamide (LSD–25) psychosis in man.

210. Isbell, H., Miner, E.J., and Logan, C.R.: Cross tolerance between *d*-2-brom-lysergic acid diethylamide (BOL–148) and the *d*-diethylamide of lysergic acid (LSD–25). *Psychopharmacologia* 1:109–116 (1959).

Simultaneous administration of 2 to 4 mg of *d*-2-brom-lysergic acid diethylamide (BOL–148) did not reduce the intensity of the reaction caused by 0.5 to 1.5 μg/kg of LSD–25. Pretreatment of eight subjects with 3 mg of BOL–148 daily for 2 days caused statistically nonsignificant reductions in all aspects of the reaction induced by 1 μg/kg of LSD–25. Pretreatment of 10 subjects with 3 mg of BOL–148 for 5 days resulted in statistically significant attenuation of all aspects of the LSD reaction that were measured. The results are more compatible with the development of cross-tolerance between BOL-148 and LSD-25 than they are with simple molecular competition between the two drugs.

211. Isbell, H., Miner, E.J., and Logan, C.R.: Relationships of psychotomimetic to antiserotonin potencies of congeners of lysergic acid diethylamide (LSD–25). *Psychopharmacologia* 1:20–28 (1959).

The psychotomimetic potency of 13 congeners of LSD–25 has been approximately determined in man. With the exception of acetylation of the indole nitrogen, all the changes made in the LSD molecule reduced psychotomimetic potency. Bromination at carbon 2 caused the greatest inactivation. High potency as a serotonin antagonist in isolated smooth muscle preparations was not correlated with high potency as a psychotomimetic. The data do not support but do not disprove the "serotonin deficiency" hypothesis of the LSD psychosis.

212. Wikler, A.: The loci and mechanisms of action of phrenotropic drugs considered in relation to screening procedures. In: Cole, J.O. and Gerard, R.W. (ed.). *Psychopharmacology: Problems in Evaluation.* pp. 213–223. Washington, D.C.: National Academy of Sciences, Publ. No. 583 (1959).

213. Wikler, A.: Narcotics. In: Braceland, F.J. (ed). *The Effect of Pharmacologic Agents on the Nervous System*. Vol. 37, Association for Research in Nervous and Mental Disease. pp. 334–335 Baltimore: Williams and Wilkins Co., 1959.

Some recent advances in our knowledge of the mechanisms of action of narcotics have been discussed in connection with (1) the use of "specific" opiate antagonists in the treatment of opiate and opioid poisoning, and in the diagnosis of narcotic addiction; (2) analgesia; and (3) problems of drug abuse. Analysis of dose-effect relationships suggest strongly that nalorphine, levallorphan, and their congeners exert their "specific" antagonistic actions against the depressive effects of narcotics by "molecular competition" at cellular (neuronal) receptor sites, and "unmasking" of the processes responsible for the opiate and opioid abstinence syndromes which may develop as a consequence of the administration of a single massive, or of repeated smaller doses of narcotic drugs. The neurophysiological mechanisms through which morphine produces "analgesia" have been analyzed mainly from the standpoint of the actions of this drug upon central processes involved in some animal "analgesic-screening" procedures that have proved to be of great empirical value. Though there are some difficulties in reconciling all of the available data, it appears that the effects of morphine upon these "analgesic-test" reflexes are exerted through selective depressant ac-

tions on interneurons in the spinal cord, coupled, perhaps, with augmentation of supraspinal (cortical and brainstem) inhibition. In addition, morphine appears to exert selective depressant actions on interneurons in the medulla, in the ascending midbrain reticular "activating" system, in the thalamic relay nuclei, and in the cerebral cortex, as well as selective excitant actions on thalamic intralaminar nuclei and the hippocampus—actions which may contribute to the genesis of the specific pattern of behavioral change that constitutes morphine "analgesia." The psychological mechanisms involved in morphine "analgesia" have been analyzed mainly from the standpoint of experimental data indicating that one of the major actions of the drug is to reduce "anxiety associated with the anticipation of pain." Problems of "drug abuse" have been analyzed from the standpoint of the hypothesis that "relapse after cure" ("habituation") is mainly a consequence of drug-seeking behavior due, initially, to reduction by the drug of "tensions" arising out of interactions between the "personality" of the user and his social milieu and, later, of new "tensions" engendered by the development of "pharmacogenic dependence" ("addiction"). The "intoxicating" ("euphoric") effects of single doses of opiates in nontolerant individuals have been considered chiefly in relation to the neurophysiological and psychological mechanisms involved in morphine "analgesia," on the assumption that these contribute also to the genesis of at least the "negative" type of morphine "euphoria." The basic neurophysiological mechanisms involved in pharmacogenic dependence (both "psychic" and "physical") appear to operate at the cellular (neuronal) level throughout the neuraxis; ablations and transections of portions of the central nervous system may alter the form of the abstinence syndrome, but they do not eliminate it. In addition to the somatic and autonomic systems, the pituitary-adrenal system is also involved in the processes of tolerance and pharmacogenic dependence. Psychologically, the "rewarding" aspects of pharmacogenic dependence are stressed, particularly with reference to alterations of motivation and the enhancement of activity directed toward new (drug-providing) goals that are consequent to the establishment of this state, and with reference to "secondary reinforcements" derived from alterations in the user's relationships to his social milieu. "Conditioning" theories that have been advanced to account for "relapse after cure" are discussed, and some recent experimental data supporting such theories are reviewed. While practically no information is available on the neurophysiological mechanisms involved in "relapse," possibilities for future research are suggested by a recent report indicating that this phenomenon, which has hitherto defied experimental investigation, can be reproduced in animals.

1960

214. Essig, C.F.: Hindlimb paresis in cats following barbital withdrawal convulsions. In: Marrazzi, A.S. and Aprison, M.H. (eds.): *Studies of Function in Health and Disease.* Galesburg, Ill.: Galesburg State Research Hospital Press, 1960.

215. Fraser, H.F. and Isbell, H.: Human pharmacology and addiction liabilities of phenazocine and levophenacylmorphan. *Bulletin on Narcotics* 12:15–23 (1960).

The human pharmacology including addictiveness of *dl*-2′-hydroxy-5,9-dimethyl-2-(2-phenethyl)-6,7-benzmorphan HBr (NIH–7519) and *l*-3-hydroxy-N-phenacylmorphinan methane sulfonate (NIH–7525) have been evaluated. In single doses given by both the intravenous and subcutaneous routes, NIH–7519 and NIH–7525 are more potent than morphine in inducing subjective effects (euphoria), in provoking morphinelike behavior, and in constricting the pupils. Both NIH–7519 and NIH–7525 are potent suppressors of the morphine abstinence syndrome, and are completely adequate substitutes for morphine in addicted persons. When the dosage of NIH–7519 and NIH–7525 was rapidly accelerated during chronic administration (addictive schedule), the overall pattern, including side effects of both, was similar to that of morphine, except that it was not feasible to increase the dosage of NIH–7519 and NIH–7525 (especially the former) as rapidly as that of morphine. Following withdrawal of NIH–7519 and NIH–7525, after substitution for morphine or after direct addiction, definite morphinelike abstinence phenomena appeared, which tended to be less severe than abstinence following withdrawal of equivalent amounts of morphine.

216. Fraser, H.F. and Isbell, H.: Pharmacology and addiction liability of *dl*- and *d*-propoxyphene. *Bulletin on Narcotics* 12:9–14 (1960).

Administration of single doses of propoxyphene (50 to 1,000 mg orally) or of *d*-propoxyphene (50 to 650 mg orally or 5 to 60 mg subcutaneously) did not induce a full pattern of morphinelike subjective effects or behavioural changes. Sedation, miosis, depression or respiratory minute volume, nausea, and vomiting were observed with the higher doses of both drugs. When substituted for morphine for 24 hours in addicted patients, both propoxyphene (1,200–2,400 mg orally daily) and *d*-propoxyphene (800 mg daily) partially suppressed symptoms of abstinence from morphine. When substituted for mor-

phine for 14 days, *d*-propoxyphene partially suppressed abstinence, but was much less effective than codeine. Following withdrawal of *d*-propoxyphene, there was no significant change in the intensity of abstinence, whereas after withdrawal of codeine, intensity of abstinence increased very significantly. Attempts to suppress completely abstinence from morphine with high dosages of *d*-propoxyphene (900 to 1,200 mg daily) were associated with a severe toxic psychosis that was readily reversed by a reduction in dosage. Two of 5 patients who received propoxyphene chronically withdrew from the experiment; 3 patients continued after the daily dosage was reduced from 1,200 to 700–850 mg daily; patients disliked the drug because of disagreeable side effects; 10 mg of nalorphine did not precipitate definite abstinence; following withdrawal of propoxyphene, only minimal abstinence was observed. In five patients *d*-propoxyphene was administered chronically in high dosage (600–825 mg daily) for 53 days. Early in this experiment, subjective effects and behavior partially resembling those seen after morphine were observed; these rapidly subsided. After withdrawal of *d*-propoxyphene, only minimal symptoms of abstinence were observed. The addiction liabilities of propoxyphene and *d*-propoxyphene are substantially less than that of codeine.

217. Fraser, H.F., Isbell, H., and Van Horn, G.D.: Human pharmacology and addiction liability of norcodeine. *The Journal of Pharmacology and Experimental Therapeutics* 129:172–177 (1960).

Codeine sulfate and norcodeine hydrocholoride administered orally have been compared in respect to their human pharmacology and addiction liabilities. In single doses of 75 mg/80 kg orally, both codeine and norcodeine induced mild to moderate morphinelike effects, and as compared to a placebo, both slightly depressed rectal temperature, respiratory rate, respiratory minute-volume, and constricted the pupils. When five successive oral doses of both drugs were given effects again were very similar. When an average of 940 mg of norcodeine daily was substituted orally for morphine in patients addicted to an average of 230 mg of morphine sulfate daily, abstinence was effectively suppressed. In direct addiction tests, tolerance to the intoxicating properties of norcodeine developed more slowly than did tolerance to similar effects of codeine. After 18 days of addiction, the average daily dosage of codeine sulfate attained was 1,485 mg, whereas the average dosage of norcodeine hydrochloride was only 400 mg. After 30 to 45 days of addiction to either codeine or norcodeine, 3 mg of nalorphine precipitated mild to moderate abstinence. When norcodeine and codeine were discontinued abruptly after 60 days of addiction, the abstinence syndrome which

developed was much milder after withdrawal of norcodeine than after withdrawal of codeine. Norcodeine possesses addictive properties, but these are significantly less than those of codeine in respect to the degree of physical dependence which develops.

218. Fraser, H.F., Isbell, H., and Wolbach, A.B.: Addictiveness of new synthetic analgesics. I. Benzimidazole derivatives: (a) 2-(p-chlorobenzyl)-1-diethylaminoethyl-5-nitrobenzimidazole methane sulfonate (NIH–7586, Ciba Ba 19,390/A, ARC I–G–1); (b) 2-(p-ethoxybenzyl)-1-diethylaminoethyl-5-nitrobenzimidazole hydrochloride (NIH–7607, Ciba–20,684, ARC I–G–2). II. (-) 3-hydroxy-N-(3,3-dimethylallyl)-morphinan hydrobromide (NIH–7446). III. (a) N-(1-methyl-2-piperidinoethyl)-propioanilide hydrochloride (Phenampromid); (b) N-[2-([methyl]-phenethylamino)-propyl]-propioanilide sulfate (Diampromid). *Committee on Drug Addiction and Narcotics.* Washington, D.C.: National Academy of Sciences, National Research Council, 1960.

219. Fraser, H.F., Van Horn, G.D., Martin, W.R., and Isbell, H.: New methods for evaluating addiction liability of morphinelike drugs. I. Attitude of opiate addicts towards drugs. II. Short-term direct addiction procedure. *Committee on Drug Addiction and Narcotics.* Washington, D.C.: National Academy of Sciences, National Research Council, 1960.

I. *Attitude of Opiate Addicts Towards Drugs.*—A method has been developed for quantifying the "attitude" of addicts toward opiate-like drugs when administered in single or chronic dosages. Questionnaires were used which provided for independent ratings by patients and observers. In the case of single doses, there was good agreement between patients' and observers' ratings of opiatelike drugs. Although potent opiates given subcutaneously and chronically were classified by both patients and observers in a comparable manner, the weaker ones were divergently described, particularly when given orally. Patients discriminated between drugs to a greater extent than did the observers, and in a manner which corresponded better with abuse rates. However, before a statement can be made about the relative reliability of patients and observers in predicting abuse-hazards by these procedures, many more drugs must be evaluated by diverse routes of administration and employing a larger sample of the addict population.

II. *Short-term Direct Addiction Procedure.*—A short "double-blind" direct addiction, crossover procedure of 18 to 20 days is satisfactory for developing significant degrees of physical dependence in the case of potent opiatelike drugs, but additional studies are necessary to determine its reliability for predicting the degree of physical dependence

induced by weak compounds. Intensity of abstinence has been evaluated for several drugs, using (a) "standard" Himmelsbach procedure in which daily point scores are computed from averages of rectal temperature, blood pressure, and caloric intake observed during the last 7 days on drugs, and (b) "modified" Himmelsbach scores computed from these measurements while the same patients were receiving placebos for 30 days. The effects of several opiatelike drugs have been compared with those of a placebo in respect to their influence on hours of "inactivity" (hours lying horizontally on the bed regardless of whether or not the patient is sleeping).

220. Hill, H.E., Haertzen, C.A., and Glaser, R.: Personality characteristics of narcotic addicts as indicated by the MMPI. *Journal of General Psychology* 62:127–139 (1960).

Using the responses of 270 hospitalized narcotic addicts to the MMPI, the present study compared the composite profiles produced by (a) a "teenage" group, (b) a white group, and (c) a Negro group. The investigation also delineated three personality subgroups in the combined Negro and white sample of adult addicts. Except for a small number of individuals it was found that all groups and subgroups of this study produced abnormal composite profiles and that one deviation they possessed in common was a T-score of 70 on the Psychopathic deviate scale. The adolescent subjects produced as deviant profiles as did the adult addicts. Using Conduct Disorder as the generic grouping and classifying profiles according to two high-point codes as, (a) Neurotic, (b) Psychopathic, or (c) Schizoid resulted in differentiable, abnormal, composite profiles. The present data and ancillary evidence provided the basis for several conclusions: (a) Personality characteristics of narcotic addicts are either associated with psychopathy or are predominantly psychopathic in nature, although they may include many of the classical psychoneurotic and psychotic features. (b) As indicated by the MMPI, personality characteristics of hospitalized adolescent addicts do not differ appreciably from those of adult addicts. (c) This similarity and the similarity between adolescent addicts and nonaddict delinquents suggest that psychopathology has considerable significance in the etiology of addiction.

221. Isbell, H.: The pharmacology of the opiates and similar addiction-producing drugs. *Proceedings of the Royal Society of Medicine* 53:925–926 (1960).

A classification of addicting drugs is presented. Such drugs are divided into two types; those that create physical dependence and those

that do not. Two types of physical dependence are known: the opiate and opioid type and the alcohol-barbiturate. Drugs that create emotional but not physical dependence include cocaine, marihuana, the central stimulants, bromides, and the major tranquilizers. Chronic taking of morphine or similar drugs results in hyperactivity in multineuronal arcs throughout the central nervous system which is unmasked by abrupt withdrawal of morphine and thus accounting for abstinence symptoms.

222. Martin, W.R.: Book review: *Problems of Addiction and Habituation.* Hoch, P.H. and Zubin, J. (eds.). 250 pp. New York and London: Grune and Stratton, 1958. *Journal of Nervous and Mental Disease* 131:455–456 (1960).

223. Martin, W.R. and Eades, C.G.: A comparative study of the effect of drugs on activating and vasomotor responses evoked by midbrain stimulation: atropine, pentobarbital, chlorpromazine, and chlorpromazine sulfoxide. *Psychopharmacologia* 1:303–335 (1960).

A method for the quantification of the effects of drugs upon the EEG and the EEG activating response using an Offner frequency analyser has been presented. The activating response has been shown to be graded in three respects: (1) latency of onset, (2) degree of depression of certain brain waves, and (3) degree of acceleration of frequency of certain brain waves. Using the degree of depression of activity of brain waves in the frequency range of 1.5 to 3.5 c.p.s. by graded stimuli to the midbrain reticular formation, it was possible to obtain estimates of the effect of drugs on the excitability and reactivity of the activating response. Simultaneous estimates of the excitability and reactivity of vasopressor responses to midbrain stimulation were obtained. Both the ascending activating system and descending vasomotor system seem to involve a muscarinic (atropine sensitive) synapse, however, evidence has been presented that, in addition to pathways involving a muscarinic synapse, these functions can be mediated over pathways devoid of muscarinic synapses. Comparing activation patterns obtained in the presence of atropine with those obtained in the presence of pentobarbital, it has been possible to dissociate two effects of activation on spontaneous cortical potentials: (1) inhibition or depression of cortical waves, and (2) acceleration of frequency of cortical waves. Both of these effects appear to be graded. Evidence has been presented indicating that the high-voltage fast activity observed after small to moderate doses of barbiturates may represent spindle activity that has been accelerated by the activating system. Chlorpromazine and chlorpromazine sulfoxide

were found to decrease the excitability of both the ascending activating system and the descending vasomotor system. The depression of excitability was better correlated with the adrenergic potentiating property of these agents than with their adrenergic blocking activity. Atropine, chlorpromazine, and chlorpromazine sulfoxide were found to increase both threshold and reactivity of the ascending activating system.

224. Martin, W.R., Riehl, J.L., and Unna, K.R.: Chlorpromazine. III. The effects of chlorpromazine and chlorpromazine sulfoxide on vascular responses to *l*-epinephrine and levarterenol. *The Journal of Pharmacology and Experimental Therapeutics* 130:37–45 (1960).

Chlorpromazine has been characterized with rabbit aortic strips as a slowly reversible adrenergic blocking agent. Chlorpromazine increased the magnitude and markedly prolonged the pressor response to levarterenol while depressing the magnitude of the response to *l*-epinephrine. Chlorpromazine sulfoxide enhanced the magnitude and prolonged the duration of the levarterenol-induced blood pressure rises and tachycardia; it prolonged the duration of *l*-epinephrine-evoked tachycardia and pressor responses. It has been proposed that chlorpromazine has two dissociable actions on epinephrine and levarterenol. It (1) blocks the adrenergic receptor and (2) depresses some deactivating process. Chlorpromazine did not significantly alter the uptake of either *l*-epinephrine or levarterenol by the red blood cell; it did not significantly alter inactivation of these amines by liver slices.

225. Wikler, A., Green, P.C., Smith, H.D., and Pescor, F.T.: Use of a dilute aqueous solution (5 μg/ml) of a benzimidazole derivative with potent morphinelike actions orally as a presumptive reinforcing agent in conditioning of drug-seeking behavior in the rat. *Committee on Drug Addiction and Narcotics.* Washington, D.C.: National Academy of Sciences, National Research Council, 1960.

Evidence in the literature is reviewed supporting the concept that, in part at least, relapse is due to conditioning factors, both of the "classical" and "instrumental" variety operating during previous episodes of addiction to narcotic drugs. The morphinelike properties of a new benzimidazole derivative (NIH–7607, ARC I–O–2) are described and evidence is presented that neither morphine addicted nor control rats display either preference for or aversion to a 5 μg/ml aqueous solution of the drug, *without discriminative training.* Two studies in progress are described in which this concentration of I–G–2 is being used as a reinforcing agent in attempts to condition drug-seeking behavior in rats.

1961

226. Eisenman, A.J., Fraser, H.F., and Brooks, J.W.: Urinary excretion and plasma levels of 17-hydroxycorticosteroids during a cycle of addiction to morphine. *The Journal of Pharmacology and Experimental Therapeutics* 132:226–231 (1961).

Two single injections of 0.6 and 0.8 and 0.6 and 0.9 mg/kg of morphine to each of 2 nontolerant men did not significantly change plasma levels or urinary excretion of 17–OHCS. The variations in plasma levels of 17–OHCS during the morning hours have been determined during addiction to morphine and during control periods. During addiction, the values observed from 6 to 10 a.m. were only 34 percent of the control levels. During addiction 17–OHCS urinary excretion was depressed to 50 percent of levels observed during control periods, a decrement of about 4 mg daily. Withdrawal of morphine was followed by tremendous increases in both plasma and urinary 17–OHCS. Such high levels of plasma 17–OHCS were reduced to control values within hours after the administration of morphine. Without medication, the level did not return to normal for several days. Although the preinjection level of plasma 17–OHCS was much lower during addiction than during control, intravenous injection of 30 IU of ACTH caused a sharp increase in the concentration of 17–OHCS in plasma during both control and addiction periods. Urinary 17–OHCS is variably increased after the injection of ACTH during control and addiction periods. The rate of disappearance of hydrocortisone from plasma, expressed as the half-life of infused hydrocortisone, was not significantly different during addiction and control phases. These experiments indicate that the lower excretion of 17–OHCS during addiction is due to their decreased production rather than to increased destruction. During addiction, adrenocortical function is depressed, but it is still capable of maximal response to direct stimulation by exogenous ACTH.

227. Essig, C.F. and Flanary, H.G.: Convulsive aspects of barbital sodium withdrawal in the cat. *Experimental Neurology* 3:149–159 (1961).

Six cats received gradually increasing amounts of barbital sodium until final dose levels of 190 to 335 mg per kilogram were reached in 106 to 267 days. Extradural electrodes were implanted in the skull to monitor the EEG during intoxication and withdrawal. During intoxication fast frequencies of 18 to 34 c/sec, such as those observed in the human EEG during barbiturate use, were present when the animals demonstrated waking, but not sleeping, behavior. Following abrupt withdrawal, five of the cats developed interseizure paroxysmal EEG abnormalities. The interseizure EEG abnormalities occurred commonly

during drowsing, and they were bilaterally symmetrical. Minor seizure behaviors were frequently observed during the occurrence of these transient EEG changes. Records were obtained on two animals at onset, and during major withdrawal convulsions. In both cases the associated EEG changes were abrupt, symmetrical, and generalized at seizure onset. The cerebral cortex appears to participate in the convulsive process, but its order of involvement may be secondary to that of the brain stem.

228. Essig, C.F., Groce, M.E., and Williamson, E.L.: Reversible elevation of electroconvulsive threshold and occurrence of spontaneous convulsions upon repeated electrical stimulation of the cat brain. *Experimental Neurology* 4:37–47 (1961).

Repeated electroconvulsive threshold determinations were made in eight cats. A Grass S–4 stimulator was used to deliver current to the epidural surface of each suprasylvian gyrus via platinum-wire electrodes imbedded in nylon stems that were firmly fixed in the skull. Thresholds were measured once or twice daily for periods of 19 to 115 days by delivering biphasic pulses 2 ms in duration for 5 s at a rate of 200 per second. Stimulation intensity was increased in steps of 3 volts at 5-min intervals until a major convulsion occurred. Threshold measurements increased 19.9 to 144 percent, or from 1 + to 9 + mA. Determination of a threshold, and induction of a suprathreshold convulsion twice daily seemed to increase the rate of threshold elevation. Three cats developed spontaneous convulsions after thresholds had increased during the last one-third of the period that regular threshold determinations were made, but none was recorded beyond the first day after daily determination of these measures was discontinued. Cessation of daily stimulation resulted in a variable but definite return toward original threshold levels. In six of the cats, determinations made at intervals of 3 days or more for periods from 3 to 8.5 weeks revealed that threshold measurements decreased from approximately 2 to 6 mA, a percentage decrease of 36.7 to 100. Histological studies of electrode sites in the cerebral cortex of two cats that had electrodes implanted revealed no demonstrable differences between the one that received daily stimulation and the one that did not.

229. Fraser, H.F., Essig, C.F., and Wolbach, A.B.: Evaluation of carisoprodol and phenyramidol for addictiveness. *Bulletin on Narcotics* 13:3–7 (1961).

The addictiveness of orally administered carisoprodol and phenyramidol has been studied in former opiate addicts. The procedures included effects of single doses, substitution tests to suppress abstinence from morphine, and direct addiction tests. It is concluded

that neither carisoprodol nor phenyramidol possess addictive qualities of an opiate type.

230. Fraser, H.F. and Isbell, H.: Human pharmacology and addictiveness of certain dextroisomers of opiates. 1. *d*-3-hydroxy-N-phenethylmorphinan, 2. *d*-3-methoxy-N-phenethylmorphinan, 3. *d*-methadone. *Committee on Drug Addiction and Narcotics.* Washington, D.C.: National Academy of Sciences, National Research Council, 1961.

231. Fraser, H.F. and Isbell, H.: Human pharmacology and addictiveness of ethyl 1-(3-cyano-3,3-phenylpropyl)-4-phenyl-4-piperidine carboxylate hydrochloride (R–1132, Diphenoxylate). *Bulletin on Narcotics* 13:29–43 (1961).

Administration of single oral, subcutaneous, or intravenous doses of R–1132 in the therapeutic range did not induce morphinelike subjective effects or behavioural changes. However, in a dose range of from 40 to 60 mg R–1132 provoked definite morphinelike euphoria and behavioural changes by the oral and intravenous routes. When given subcutaneously in doses of 5 to 50 mg, only minimal effects were observed. When substituted for morphine for 24 hours in addicted patients, it suppressed abstinence from morphine practically completely, and the dosage equivalence was considered to be 1 mg of morphine for 1.8 mg of R–1132. When substituted for morphine for a period of 10 successive days, R–1132 was slightly more effective than codeine in preventing the appearance of abstinence phenomena, but it was not identified as an opiate during the interval of substitution. Abrupt withdrawal of R–1132 resulted in a milder abstinence syndrome than that which occurs after abrupt withdrawal of codeine, following substitution of the latter in equivalent morphine abstinence-suppressing dosages. Five patients received oral doses of R–1132 chronically for 45 to 61 days, and the dosage was gradually and carefully increased as tolerance developed until the average maximum dosage attained was 188 mg daily. In another "double-blind" crossover study, eight patients received orally R–1132, morphine, and codeine, all given in a rapidly accelerated dosage for 18 to 20 days, and the effects were compared with a placebo. Objectively, especially on the more rapidly increasing dosage schedule of R–1132, the overall pattern of behaviour resembled that of addiction to morphine or codeine, except that sedative effects were more prominent. In both of these tests, however, the patients were much more impressed with the sedative rather than the opiate characteristics of R–1132. When R–1132 was abruptly discontinued in both of these studies, a definite but mild abstinence syndrome developed, which was significantly less severe than that observed when oral morphine was withdrawn from the same patients, but comparable to the abstinence

syndrome that ensued after abrupt withdrawal of oral codeine. When R–1132 was administered chronically in high dosage, nalorphine precipitated a moderately severe abstinence syndrome. When R–1132 and codeine were continuously administered in high and euphorogenic dosages at different times for 5 consecutive days, both drugs were identified consistently as an opiate (dope), and the effects of both drugs were liked by the patients. It is concluded that R–1132 possesses abuse liability. Considering all the data available, it appears that this is definitely less than that of morphine and greater than that of *d*-propoxyphene. Although the abuse liability of R–1132 is comparable with that of codeine in several respects, the unsuitability of R–1132 for parenteral injection decreases the hazards that may attend its use in clinical practice.

232. Fraser, H.F., Martin, W.R., Wolbach, A.B., and Isbell, H.: Addiction liability of an isoquinoline analgesic, 1-(p-chlorophenethyl)-2-methyl-6, 7-dimethoxy-1, 2, 3, 4-tetrahydroisoquinoline. *Clinical Pharmacology and Therapeutics* 2:287–299 (1961).

The addictiveness of I–K–1 has been compared with the liability of morphine, codeine, and D-propoxyphene in former opiate addicts. Single oral doses of 600 and 1,200 mg of I–K–1 (10 to 17 times the recommended analgesic dose) did not induce subjective or objective patterns of morphinelike effects in nontolerant former opiate addicts, but 400 mg intramuscularly was identified as an opiate by 5 of 6 nontolerant subjects. Single intravenous doses of 60 and 120 mg of I–K–1 produced effects comparable to those of identical doses of codeine and D-propoxyphene in nontolerant subjects, but 180 mg of I–K–1 was less effective than 180 mg of D-propoxyphene in partially tolerant opiate addicts. Oral, intravenous, and intramuscular I–K–1 partially suppressed signs and symptoms of abstinence from morphine. Intramuscularly, I–K–1 was only about one-seventh as potent as codeine in this respect. In a direct addiction test of 60 days, using maximally tolerated doses (750 to 1,500 mg orally daily), I–K–1 was disliked by former addicts, and when I–K–1 was discontinued abruptly, withdrawal signs were insignificant. An attempt was made to ascertain the addiction liability of I–K–1 by injection using a short addiction test of 7 days and comparing I–K–1 with morphine, codeine, and D-propoxyphene. Insofar as I–K–1 was concerned, it was necessary to terminate the experiment after the drug had been administered intravenously to three patients and to one intramuscularly because of the marked inflammation at the site of injection (it required a pH of about 3 to maintain I–K–1 in solution). 1-(*p*-Chlorophenethyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, it is concluded, has substantially less addiction liability than morphine and codeine and even less addictiveness than D-propoxyphene.

233. Fraser, H.F., Martin, W.R., Wolbach, A.B., and Isbell, H.: Addiction liability of 1-(p-chlorophenethyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (I–K–1, Ro 4–1778/1). *Committee on Drug Addiction and Narcotics.* Washington, D.C.: National Academy of Sciences, National Research Council, 1961.

1-(p-Chlorophenethyl)-2-methyl-6,7-dimethoxy-1,2,3,4,-tetrahydroisoquinoline (I–K–1) has substantially less addiction liability than morphine and codeine, and even less addictiveness than *d*-propoxyphene.

234. Fraser, H.F., Van Horn, G.D., Martin, W.R., Wolbach, A.B., and Isbell, H.: Methods for evaluating liability. (A) "Attitude" of opiate addicts toward opiatelike drugs. (B) A short-term "direct" addiction test. *The Journal of Pharmacology and Experimental Therapeutics* 133:371–387 (1961).

A method has been developed for quantifying the "attitude" of addicts toward opiatelike drugs when administered in single or chronic dosages. Questionnaires were used which provided for independently prepared ratings by patients and observers. In single doses, the effects of weak morphinelike drugs were readily differentiated from those of a placebo by both patients and aides. After single doses, the ratings of patients and observers were in good agreement; however, observers gave higher ratings than patients particularly on the parameters of "feel drug," identification of "dope," and degree of "liking." Although potent opiates given chronically by the subcutaneous route were classified by both patients and observers in a comparable manner, those given orally were divergently described. Both patients and observers readily differentiated a placebo from weak morphinelike drugs. Patients discriminated between drugs and route of administration to a greater extent than did observers, and in a manner which corresponded better with abuse rates for heroin, morphine, and codeine. However, before a statement can be made about the relative validity of patients' and observers' ratings, many more drugs must be evaluated by diverse routes of administration and employing a larger sample of the addict population. A short, "doubleblind," direct addiction, crossover procedure of 18 to 20 days is satisfactory for developing significant degrees of physical dependence in the case of morphine and codeinelike drugs, but additional studies are necessary to determine its reliability for assessing the degree of physical dependence induced by weak compounds and compounds in the methadone and meperidine series.

235. Fraser, H.F. and Wolbach, A.B.: The addiction liability of alpha-*dl*-3-acetoxy-4,4-diphenyl-6-methylamino-heptane hydrochloride (NIH–7667, ARC I–C–25) and 6-acetyl-3-

ethoxydihydromorphine (NIH–7623, ARC I–A–38). *Committee on Drug Addiction and Narcotics.* Washington, D.C.: National Academy of Sciences, National Research Council, 1961.

236. Isbell, H.: Drug addiction (pharmacopsychosis, morphine, or other drug habit; morphinism; cocainism; barbiturism). *The Merck Manual* (ed. 10). Rahway, N.J.: Merck Sharp & Dohme Research Laboratories, 1961.

237. Isbell, H.: Perspectives in research on opiate addiction. *British Journal of Addiction* 57:17–29 (1961).

Opiate addiction is a complex problem involving the interaction of socioeconomic, psychological, pharmacological, and physiological factors. Basic research in all these areas is needed for better understanding of the problems. In the United States the highest incidence of opiate addiction occurs in problem areas of large cities and involves chiefly minority ethnic groups. The incidence of social problems other than opiate addiction is also high in such areas. The chief psychiatric condition associated with opiate addiction is the character disorder. The most satisfactory psychological theory is that of Wikler which is based on conditioning of abstinence. All derivatives of morphine and all synthetic drugs with a spectrum of morphinelike actions are addicting. The most promising lead for a nonaddicting analgesic is the narcotic antagonist. Some of these drugs are analgesics. They will not support physical dependence qualitatively different from that on morphine. Research on such compounds should be pressed vigorously. Physical dependence on morphine is a real physiological disturbance in the central nervous system. It is diffuse and affects all levels from the spinal cord to the cerebral cortex and is associated with hyperactivity in multineuronal areas which is unmasked when drugs are withdrawn. Continuing investigation of the changes on individual neurones during addiction and of the biochemical changes in neurones and in synapses should be fruitful.

238. Isbell, H., Wolbach, A.B., Wikler, A., and Miner, E.J.: Cross tolerance between LSD and psilocybin. *Psychopharmacologia* 2:147–159 (1961).

In two experiments, using a crossover design, the development of "direct" tolerance to LSD and psilocybin was measured after 10 (experiment I) or 9 (experiment II) volunteers had taken LSD in doses measuring to 1.5 μg/kg over the course of 6–7 days (experiment I) or 13 days (experiment II). On another occasion, the same patients received psilocybin in doses increasing to 150 μg/kg over the course of 6–7 days (experiment I) or 210 μg/kg over the course of 13 days (experiment II). The development of "cross" tolerance to psilocybin in patients "directly"

tolerant to LSD was measured by "challenging" the patients after they had received LSD chronically, with 150 μg/kg (experiment I) or 210 μg/kg (experiment II) of psilocybin. "Cross" tolerance to LSD was evaluated by "challenging" the patients, after they had received psilocybin chronically with 1.5 μg/kg of LSD. A high degree of "direct" tolerance to LSD developed in both experiments, as manifested by statistically significant reductions in six of the seven parameters of response. Patients "directly" tolerant to LSD were also "cross" tolerant to psilocybin on five (experiment I) or four (experiment II) parameters. Definite "direct" tolerance also developed after chronic administration of psilocybin in both experiments, but statistically significant reductions occurred in fewer parameters of response (four in experiment I and three in experiment II) than was the case with LSD. Patients chronically treated with psilocybin were also "cross" tolerant to LSD on four (experiment I) or three (experiment II) measurements. The degree of "direct" tolerance to psilocybin was less than the degree of "direct" tolerance to LSD. The development of "cross" tolerance between LSD and psilocybin reinforces the idea that these two drugs cause psychic disturbances by acting on some common mechanism, or on mechanisms acting through a common final pathway.

239. Martin, W.R. and Eades, C.G.: Demonstration of tolerance and physical dependence in the dog following a short-term infusion of morphine. *The Journal of Pharmacology and Experimental Therapeutics* 133:262–270 (1961).

An 8-hour infusion of morphine has been used to produce a demonstrable degree of physical dependence and tolerance in the dog. Physical dependence has been unmasked by nalorphine and the syndrome produced by this procedure is distinct, reproducible, and consists of restlessness, apprehension, violent tremors, lacrimation, salivation, rhinorrhea, urination, defecation, vomiting, mydriasis, and tachycardia. Tolerance is readily discernible during the course of infusion and can be clearly demonstrated the day following infusion, using a standard test dose of morphine. Tolerance to behavioral depression (narcosis), depression of the skin twitch, and withdrawal reflex is marked. The reproducibility and brevity of this method may recommend it for preliminary screening of analgesic agents to identify those that produce physical dependence.

240. Martin, W.R. and Fraser, H.F.: A comparative study of physiological and subjective effects of heroin and morphine administered intravenously in postaddicts. *The Journal of Pharmacology and Experimental Therapeutics* 133:388–399 (1961).

Using a variety of subjective and objective measures, the relative

potency of heroin to morphine administered intravenously to post-addicts found 1.80 to 2.66 mg of morphine sulfate equal to 1 mg of heroin. In addition, it was found that postaddicts could identify heroin and morphine as such with a high degree of accuracy when these agents were administered intravenously either on an acute or chronic basis. Though postaddicts showed no preference for one or the other of these drugs when administered on a single injection basis, five out of eight expressed a preference for heroin in the short-term addiction study. However, on the basis of postaddicts' reports on "the most important effects of morphine and heroin," no constellation of effects could be discerned that explained the preference for heroin. Equipotent doses of these drugs had quite comparable time-action courses when administered intravenously, and on this basis there was no marked difference in their ability to produce feelings of "euphoria," ambition, nervousness, relaxation, drowsiness, or sleepiness. Although the heroin abstinence syndrome was of shorter duration than that of morphine, the peak intensity was quite comparable for the two drugs. Data acquired during short-term addiction studies did not support the statement that tolerance develops more rapidly to heroin than to morphine. These findings have been discussed in relation to the physicochemical properties of heroin and morphine and the metabolism of heroin.

241. Wikler, A.: On the nature of addiction and habituation. *British Journal of Addiction* 57:73–80 (1961).

242. Yamahiro, R.S., Bell, E.C., and Hill, H.E.: The effects of reserpine on a strongly conditioned emotional response. *Psychopharmacologia* 2:197–202 (1961).

Twenty-six Wistar albino rats were conditioned to inhibit a lever-pressing response during a 4-minute tone period which was terminated by a strong electric shock (CER). Two groups of 10 animals, matched on the basis of rate during the pretone and tone periods, were tested concurrently throughout the experiment. The experimental group was administered a daily and periodically increasing dose of reserpine (0.2–0.6 mg/kg) for a period of 18 consecutive days. It was found that reserpine produced no significant effects on the CER when compared with that of the matched control group, although an increase in the restoration of lever pressing as a function of time was found to be significant for both groups. It was concluded that the partial restoration of the lever-pressing response with time was a function of partial extinction of the CER, and that reserpine does not significantly reduce a strongly conditioned emotional response.

1962

243. Essig, C.F. and Carter, W.W.: Failure of diphenylhydantoin in preventing barbiturate withdrawal convulsions in the dog. *Neurology* 12:481–484 (1962).

Beagle and miniature dogs, made dependent on 106–195 mg/kg of barbital, were abruptly withdrawn; 11 of 15 control dogs had grand mal convulsions and 4 of the 15 control dogs died following abrupt withdrawal of barbital. Of the 16 dogs treated with diphenylhydantoin, 11 had grand mal convulsions and 5 died during barbital withdrawal. Thus in the dog, diphenylhydantoin does not appear to prevent barbiturate withdrawal convulsions and associated death.

244. Essig, C.F.: Convulsive and sham rage behaviors in decorticate dogs during barbiturate withdrawal. *Archives of Neurology* 7:471–475 (1962).

Three decorticate dogs and their intact controls received increasing amounts of barbital sodium until final daily dose levels of 118 to 178 mg per kg were attained. Following abrupt withdrawal, all of the control dogs, but none of the decorticate dogs, developed tonic-clonic convulsions. One decorticate dog exhibited two episodes of sham rage behavior that included violent motor activity, barking, trembling, and excess salivation. Two of the decorticate dogs were intoxicated and withdrawn a second time. Final daily dose levels attained were 190 and 248 mg per kg, and both these preparations developed sham rage as well as convulsive behavior during the second withdrawal. The seizure patterns were modified in comparison to intact dogs, and it was concluded that the decorticate dog requires higher final intoxication levels of barbiturate than the intact animal in order to develop abstinence convulsions that are not as intense. In the intact brain the cerebral cortex probably plays a facilitatory role in barbiturate convulsions, but it does not seem to be a necessary site of their origin or an obligatory substrate thereof.

245. Essig, C.F.: Focal convulsions during barbiturate abstinence in dogs with cerebrocortical lesions. *Psychopharmacologia* 3:432–437 (1962).

In contrast to cerebrocortical lesions induced by a freezing technique, those due to multiple injections of aluminum hydroxide were associated with both focal and generalized convulsions in miniature dogs following abrupt withdrawal of increasing doses of barbital sodium. These withdrawal phenomena appeared after final dose levels of barbiturate comparable to those associated with generalized abstinence convulsions in normal dogs.

246. Fraser, H.F. and Isbell, H.: Human pharmacology and addictiveness of certain dextroisomers of synthetic analgesics: I. *d*-3-hydroxy-N-phenethylmorphinan, II. *d*-3-methoxy-N-phenethylmorphinan, III. *d*-methadone. *Bulletin on Narcotics* 14:25–35 (1962).

I. *d*-3-hydroxy-N-phenethylmorphinan. This compound was evaluated for addictiveness by administering single doses subcutaneously and orally and by 24-hour substitution tests in patients dependent on morphine. Conclusion: In the doses employed, *d*-3-hydroxy-N-phenethylmorphinan hydrobromide showed no evidence of opiate type of addictiveness.

II. *d*-3-methoxy-N-phenethylmorphinan tartrate (7296A). This compound was evaluated for addictiveness by administration of single doses, 24-hour substitution tests in patients dependent on morphine, and by direct addiction tests. Conclusion: The addictiveness of *d*-3-methoxy-N-phenethylmorphinan (7296A) is minimal and is substantially less than that of codeine.

III. *d*-methadone hydrochloride. This compound was evaluated for addictiveness by single dose tests subcutaneously and orally, by oral substitution tests for 24 hours in patients dependent on morphine, and by direct addiction tests orally. Conclusion: *d*-Methadone, if given in adequate doses, induces morphinelike subjective effects, partially suppresses abstinence in morphine dependent subjects, and creates a mild degree of physical dependence. Therefore, it has morphinelike addictive properties. Overall, however, it is considered to have less abuse potential than codeine.

247. Hill, H.E.: The social deviant and initial addiction to narcotics and alcohol. *Quarterly Journal of Studies on Alcohol* 23:562–582 (1962).

To recapitulate briefly, and to integrate findings and hypothesis, a preliminary and tentative outline of the development of alcoholism and opiate addiction is presented. Of necessity, important aspects of these addictions—many similarities and differences, for instance—cannot be touched upon here. The more ready availability of alcohol and the greater acceptability of its use by the larger society is undoubtedly partially responsible for the enormity of the difference in the incidence of these addictions. However, except for such specific differences as those found in the development of tolerance to and length of action of these drugs, the following formulation would seem to apply equally to both. 1. While a lawful concurrence of events determines the "high" degree of availability of drug supplies to the social deviant, he does not initially actively seek them. 2. Deficient social controls determine acceptability to the individual of experimentation with drugs. 3. Fortuity, at least with respect to individual choice, determines the drug which will be tried initially and the circumstances under which this occurs. 4. Rein-

forcement from daily activities is inadequate, and counter-anxiety is not of sufficient strength to deter the social deviant from retrial and excessive use. This would seem to be the case regardless of the circumstances in which retrial occurs. 5. The progress of initial addiction is determined by learning and conditioning. In this process the degree of reinforcement and, therefore, the probability of repeated use are contingent upon (a) the interaction of specific effects of the drug used and the particular patterning of social and idiosyncratic responses of the individual; and (b) relief of abstinence symptoms following repeated use. 6. After sufficient periods of abstinence to eliminate measurable signs of physiological dependence, relapse occurs according to further learning principles partially described in the pharmacodynamic theory of Wikler (42). While it would seem plausible that Wikler's theoretical position could be effectively applied to alcoholism, it has not been developed in this connection. Eventually, if research in social deviance, the addictions, and psychopharmacology are sufficiently encouraging, the above working formulation will require a more rigorous development, with emphasis being placed upon the response patterning in the individual, and drug-produced shifts in the probability of the occurrence of responses in such hierarchies.

248. Hill, H.E., Haertzen, C.A., and Davis, H.: MMPI factor analytic study of alcoholics, narcotic addicts and criminals. *Quarterly Journal of Studies on Alcohol* 23:411–431 (1962).

Minnesota Multiphasic Personality Inventory (MMPI) profiles were obtained on institutionalized groups of alcoholics, narcotic addicts, and criminals, each sample being composed of 200 subjects. Application of the principal axes technique of factor analysis to the scale T-scores isolated five factors. Three of these were sufficiently well defined to produce predictable and stable personality configurations. The first factor, labeled "Undifferentiated psychopath" and interpreted as indicating uncomplicated social deviance, was characterized by a single "spike" on the Pd scale. Small, statistically significant but nondiagnostic differences were found—the criminals produced slightly greater loadings on this factor. Factor 2 was bipolar: The composite profile for the positive pole was much the same "double-spike" (Pd-Ma) pattern as was found previously in narcotic addicts; it was labeled "Primary psychopath." The negative pole was labeled "Neurotic psychopath, depressed," since it showed considerable elevation on the neurotic triad, especially on Depression, and on the Pd scale. While both factors showed strength in the three criterion groups, small but again nondiagnostic differences were found. The criminals were more numerous on the positive pole, the alcoholics more numerous on the negative pole, and the addicts were intermediate in factor loadings. Factors 3, 4, and 5

produced further evidence for the presence of classic psychopathologies, but with clear indications of social deviance (Pd elevation) in all. Suggestions were made with regard to the adoption of certain modes of adaptation by the social deviant and for further research in the addictions.

249. MARTIN, W.R. Book Review.: *Drug Addiction: Crime or Disease?* Interim and Final Reports of Joint Committee of American Bar Association and American Medical Association on Narcotic Drugs. 173 pp. Bloomington, Ind.: Indiana University Press, 1961. *Journal of Nervous and Mental Diseases* 134:488–491 (1962).

250. MARTIN, W.R. and EISENMAN, A.J.: Interactions between nalorphine and morphine in the decerebrate cat. *The Journal of Pharmacology and Experimental Therapeutics* 138:113–119 (1962).

Morphine (11 to 20 mg/kg) has been shown to decrease respiratory rate, respiratory minute volume, pulse rate and blood pressure, increase serum CO_2 concentration, and decrease serum pH in the decerebrate cat. Nalorphine (5 and 10 mg/kg), on the other hand, produces a moderate increase in respiratory rate and minute volume and a modest decrease in serum CO_2 and blood pressure. Nalorphine, when administered to decerebrate cats severely depressed by morphine, produces a transient and marked increase in respiratory rate, minute volume, blood pressure and pulse rate which gradually subsides to an equilibrium state characterized by a normal pulse rate and blood pressure and a slight tachypnea. At this equilibrium state serum CO_2 is lower than control level and serum pH is slightly elevated. Analysis of these findings indicates that there are several factors involved in the nalorphine-morphine interaction in the decerebrate cat; nalorphine exerts a direct stimulant action upon the respiratory system, antagonizes certain effects of morphine and unmasks acute physical dependence. A mechanism has been proposed and demonstrated that provides, in part, a physiological basis for acute physical dependence. These findings have also been related to the clinical effectiveness of nalorphine in various degrees of morphine intoxication.

251. O'DONNELL, J.A.: The Lexington program for narcotic addicts. *Federal Probation*, pp. 55–60, Mar. 1962.

252. SLOAN, J.W., BROOKS, J.W., EISENMAN, A.J., and MARTIN, W.R.: Comparison of the effects of single doses of morphine and thebaine on body temperature, activity, and brain and heart levels of catecholamines and serotonin. *Psychopharmacologia* 3:291–301 (1962).

An equal number of male and female rats received single doses of

15, 30, or 60 mg/kg of morphine sulfate. Most of these were sacrificed 4 hours after administration. Some of the rats receiving 60 mg/kg of morphine were sacrificed at 2 hours. Animals were pooled in groups of four, and brain and hearts were excised and analyzed for catecholamines. Brains were also analyzed for serotonin. The animals were observed for changes in "activity" and body temperature. Changes in brain catecholamines were not statistically significant in animals sacrificed 4 hours after receiving morphine. Animals sacrificed 2 hours after administration of 60 mg/kg of morphine showed statistically significant increases in brain catecholamine. No statistically significant changes appeared in brain serotonin after morphine administration. Changes in heart catecholamines were not statistically significant. Doses of 15 and 30 mg/kg resulted in an initial depression of activity followed by an increase in activity and body temperature; 60 mg/kg produced profound depression of both activity and body temperature, maximum at 2 hours. Respiratory depression also occurred in these animals and about one-half showed cyanosis. None of the rats after 15 mg/kg, and very few after 30 mg/kg, showed cyanosis. The effects of morphine were compared to those of 20 mg/kg of thebaine. Since convulsions after thebaine occurred within 20 minutes animals were sacrificed at from 30 to 60 minutes after injection. Thebaine produced a moderate decrease in brain and heart catecholamine levels, statistically significant for the heart. No significant changes in brain serotonin were observed. Fifteen of the 26 animals showed convulsive "behavior"; 7, major seizures; and 4, deaths. They appeared sedated in nonseizure intervals. Hyperthermia was not observed.

253. Wikler, A.: Drug Addiction. In: Baker, A.B. (ed.): *Clinical Neurology*, Vol. 2, pp. 1054–1083, New York City: Hoeber-Harper, 1962.

254. Wikler, A.: Drug addiction. In: Tice, F. (ed.): *Practice of Medicine*, Vol. 8 (rev.) pp. 17–58, Hagerstown, Md.: W.F. Prior Co., Inc., 1962.

255. Wolbach, A.B., Jr., Isbell, H., and Miner, E.J.: Cross tolerance between mescaline and LSD–25. With a comparison of the mescaline and LSD reactions. *Psychopharmacologia* 3:1–14 (1962).

The reactions caused by intramuscular administration of 0.75 μg/kg and 1.5 μg/kg of LSD–25 have been compared in the same 10 subjects with those induced by 2.5 mg/kg and 5.0 mg/kg of mescaline. Both LSD and mescaline caused dilatation of the pupils, increase in body temperature, elevation of pulse rate, and increase in systolic blood pressure. Both drugs decreased the threshold for elicitation of the knee jerk. After both drugs, similar abnormal mental states characterized by

anxiety, difficulty in thinking, alteration in mood (generally euphoric), altered sensory perception (particularly visual), elementary and true visual hallucinations, and alterations of body image were reported by the subjects. The effects of mescaline appeared more slowly and persisted somewhat longer than did the effects of LSD. LSD tartrate is 2,400–4,900 times as potent as mescaline hydrochloride. On a molecular basis, LSD is 4,500 to 9,275 times as potent as mescaline. Patients receiving LSD daily developed direct tolerance to LSD; such patients were also cross-tolerant to mescaline. Likewise patients receiving mescaline daily became tolerant to mescaline and cross-tolerant to LSD. It was inferred that LSD, psilocybin, and mescaline probably share common mechanisms of action or some common final pathway.

256. Wolbach, A.B., Jr., Miner, E.J., and Isbell, H.: Comparison of psilocin with psilocybin, mescaline, and LSD–25. *Psychopharmacologia* 3:219–223 (1962).

Reactions induced by LSD, mescaline, psilocin, and psilocybin are qualitatively similar. The time course of the psilocin and psilocybin reactions are shorter than those of LSD or mescaline reactions. 1 μg/kg of LSD tartrate is approximately equivalent to 45 μg/kg of psilocin; 1 μg of psilocin is approximately equivalent to 66 μg/kg of mescaline. Psilocin is approximately 1.4 times as potent as psilocybin. This ratio is the same as that of the molecular weights of the two drugs.

1963

257. Essig, C.F.: Addictive and possible toxic properties of glutethimide. *American Journal of Psychiatry* 119:993 (1963).

258. Essig, C.F.: Anticonvulsant effect of amino-oxyacetic acid during barbiturate withdrawal in the dog. *International Journal of Neuropharmacology* 2:199–204 (1963).

Substances that counteract barbiturate withdrawal convulsions in dogs are being sought as indicators of neurochemical mechanisms that might underlie the barbiturate abstience syndrome. Barbital sodium was given to 38 beagle dogs in single oral daily doses increasing from 40 to 150 mg/kg during 170 days. Following abrupt and complete withdrawal of barbital sodium, 16 dogs received only 0.9 saline solution and all of them had one or more tonic-clonic convulsions during 7 days of abstinence. Another 22 dogs were withdrawn and amino-oxyacetic acid (AOAA) was administered from the 24th through the 168th h (7 days) of abstinence at 8-h intervals in doses of 5, 8, and 11 mg/kg. Only 11 of these

22 AOAA treated dogs had one or more convulsions during 7 days of barbiturate withdrawal. AOAA causes an increase in brain gamma-amino butyric acid (GABA), a substance with anticonvulsant properties. It is not possible as yet to definitely attribute the anticonvulsant effect of AOAA to GABA accumulation in brain or to implicate that substance in the neurochemical mechanisms underlying barbiturate withdrawal, but the observations here reported do suggest that further research would be desirable.

259. Essig, C.F., Groce, M.E., and Williamson, E.L.: Electroconvulsive threshold elevation: From daily stimulation of adrenalectomized animals. *Science* 140:828–829 (1963).

The elevation of electroconvulsive threshold, which develops in cats during repeated daily measurements thereof might result from an increased production of deoxycorticosterone. Bilateral adrenalectomy followed by maintenance on deoxycorticosterone and cortisone in fixed dosages did not prevent subsequent elevation of the threshold in either cats or miniature dogs. The elevation rate in the adrenalectomized dogs exceeded that in the intact control dogs. This elevation, which resembles tolerance, in the intact cat or miniature dogs, is not dependent on an increased production of adrenocortical hormones; it may more likely be the result of cerebral rather than extracerebral adaptation.

260. Fraser, H.F., Jones, B.E., Rosenberg, D.E., and Thompson, A.K.: Effects of addiction to intravenous heroin on patterns of physical activity in man. *Clinical Pharmacology and Therapeutics* 4:188–196 (1963).

Physical activity measurements were made during 30 days of placebo administration followed by 60 days of addiction to intravenous heroin. The experimental design was double blind. Five prisoner addicts served as subjects. The daily measures of activity selected were: (a) hours lying horizontal on the bed, (b) hours of sleep, (c) hours off the research ward, and (d) miles recorded on a pedometer. The several activity measurements correlated well. The experiments indicate that techniques may be used to measure major daily activities which require minimal directed participation by the subject and which do not significantly influence degree and quality of activity. Compared with placebo, heroin increased activity when given in single intravenous doses or in repeated doses for 3 or 4 days, but depressed activity when chronically administered over a longer interval. When patients chronically received heroin they showed a pronounced tendency to retreat from all forms of activity and social contacts, and to go to their rooms to lie alone on their beds, eyes closed, frequently with radios turned on, "nodding" (sedated, but usually not sleeping). Clinical observations and pursuit rotor tests indicate that the depressant effects on activity observed during chronic

heroin administration were not due to debility or to psychomotor impairment but rather suggest a reduced responsiveness of the patient to ambient stimuli.

261. Fraser, H.F. and Rosenberg, D.E.: Observations on the human pharmacology and addictiveness of methotrimeprazine. *Clinical Pharmacology and Therapeutics* 4:596–601 (1963).

Methotrimeprazine, a derivative of chlorpromazine, has been evaluated for addictiveness by subcutaneous administration to former opiate addicts. It does not induce morphinelike effects when given in single doses, and only partially suppresses abstinence from morphine. When given chronically its effects were disliked and it did not induce physical dependence. Therefore, it does not possess morphinelike addictiveness. Sedation and postural hypotension are conspicuous pharmacologic effects of methotrimeprazine, and may greatly impair its clinical usefulness. Insofar as evaluated, rectal body temperature, respiratory rate, and systolic blood pressure (horizontal) were not affected by methotrimeprazine. No extrapyramidal symptoms were observed. All subjects retained a good appetite, and showed a moderate gain in body weight while receiving methotrimeprazine chronically.

262. Fraser, H.F. and Rosenberg, D.E.: Preliminary report on the human pharmacology and addiction liability of 2-cyclopropylmethyl-2′-hydroxy-5,9-dimethyl-6,7-benzomorphan (ARC II–C–3, WIN 20,740). *Committee on Drug Addiction and Narcotics.* Washington, D.C.: National Academy of Sciences, National Research Council, 1963.

2-Cyclopropylmethyl-2′-hydroxy-5,9-dimethyl-6,7-benzomorphan (II–C–3, Win 20,740) has been evaluated for addictiveness in former opiate addicts using crossover designed experiments in which comparisons were made with morphine or placebo. In single doses by three routes of administration (oral, subcutaneous, and intravenous) II–C–3 induced less euphoria than did morphine. When substituted for morphine in morphine-dependent subjects, it precipitated rather than suppressed abstinence. When administered chronically for 25 days to four subjects, it induced some initial dysphoria to which tolerance developed, and was seldom identified as an opiate. When II–C–3 was abruptly withdrawn after 25 days a very mild atypical abstinence syndrome developed, whereas these same patients showed moderate to severe abstinence after a comparable direct addiction to morphine.

263. Fraser, H.F. and Rosenberg, D.E.: Studies on addiction liability of 2-hydroxy-5,9-dimethyl-2-(3,3-dimethylallyl)-6,7-benzomorphan (II–C–2); a weak narcotic antagonist. *Committee on Drug Addiction and*

Narcotics. Washington, D.C.: National Academy of Sciences, National Research Council, 1963.

2′-Hydroxy-5,9-dimethyl-2-(3,3-dimethylallyl)-6,7-benzomorphan (Win 20,228) has been evaluated for addictiveness in former opiate addicts. In crossover designed experiments Win 20,228 was compared with morphine, placebo, and *d*-propoxyphene in one test. In single subcutaneous doses the effects of Win 20,228 were subjectively different from morphine and less frequently identified as an opiate. Single intravenous doses of Win 20,228 (35 mg/70 kg) showed significantly less morphinelike effects than intravenous morphine (25 mg/70 kg); and less opiate effects than *d*-propoxyphene (160 mg/70 kg). Win 20,228 was substituted for morphine in morphine-dependent subjects using the maximum tolerated and/or accepted dosage. Addicts did not like the effects induced and there was no significant suppression of abstinence signs. Chronic administration of Win 20,228 was disliked by opiate addicts. Seven of eight subjects elected to stop taking it, whereas none discontinued morphine. The eighth subject (who continued on Win 20,228 for 25 days despite a severe inflammatory reaction at injection sites) showed a mild but definite abstinence syndrome when the drug was discontinued, but no physical dependence was demonstrated by the nalorphine test. On the other hand, when morphine was chronically administered, its effects were consistently liked by all these subjects. Definite physical dependence was demonstrated by the nalorphine test, and when morphine was abruptly withdrawn the intensity of abstinence observed was much greater than that following withdrawal of Win 20,228. It is concluded from these experiments that Win 20,228 has definitely less addictiveness (abuse liability) than morphine and, insofar as the experiments may be interpreted, the degree of addictiveness approximates that of *d*-propoxyphene.

264. Fraser, H.F., Rosenberg, D.E., and Isbell, H.: Progress report of the NIMH Addiction Research Center on certain analgesis drugs. *Committee on Drug Addiction and Narcotics,* Washington, D.C.: National Academy of Sciences, National Research Council, 1963.

This is a progress report on studies of the following: I. 1-Dimethylamino-3-phenylindane hydrochloride; II. 2-amino-indane hydrochloride; III. 1-(3-Cyano-3,3-diphenylpropyl)-4-(1-piperidino)-4-piperidine carboxylic acid amide; IV. Mixture of phenazocine plus N-allynorphenazocine; V. (−)-2′Hydroxy-2,5,9-trimethyl-6,7-benzomorphan (levometazocine).

265. Haertzen, C.A.: A method for direct determination of inverted factor loadings. *Psychological Reports* 12:399–402 (1963).

A procedure is presented for the determination of orthogonal markers and for the direct calculation of inverted factor loadings. Or-

thogonal markers are determined by deviations from regression. The application of factor analysis to the analysis of similarity of profiles of individuals has been impeded because of the formidable calculations required. Once profiles exemplifying factors have been identified, these profiles can be intercorrelated. By subtracting out deviations from regression of the first factor on the second, etc., profiles for the independent portion of factors can be identified. These profiles, when correlated with the profiles of Ss., exactly duplicate loadings which would have been obtained by the diagonal method of factor analysis.

266. Haertzen, C.A. and Hill, H.E.: Assessing subjective effects of drugs: An index of carelessness and confusion for use with the Addiction Research Center Inventory (ARCI). *Journal of Clinical Psychology* 19:407–412 (1963).

A scale comprised of items that are repeated identically or in opposite form was described; the score on this Ca scale of the Addiction Research Center Inventory is the number of inconsistent responses. Comparison of Ca scores obtained under various conditions (no-drug, placebo, chlorpromazine, LSD–25, morphine, pentobarbital, amphetamine, pyrahexyl, and alcohol) shows that the scale is sensitive to some forms of drug-induced inconsistency. Comparison of these scores with the MMPI F-scale for malingering, the Shipley vocabulary test of illiteracy, and with overt signs of carelessness also indicates that the Ca scale measures certain aspects of carelessness and illiteracy. Significant proportions of the variance of Ca are accounted for by a first factor of general drug effects, and by a group factor of confusion and/or carelessness. Results indicate that a considerable degree of the "systematic inconsistency" found under some conditions is due to drug-induced alteration in response hierarchies.

267. Haertzen, C.A., Hill, H.E., and Belleville, R.E.: Development of the Addiction Research Center Inventory (ARCI): Selection of items that are sensitive to the effects of various drugs. *Psychopharmacologia* 4:155–166 (1963).

A "custom-built" inventory for assessing subjective effects of drugs, the Addiction Research Center Inventory (ARCI), was developed from the use of "sentence completion" and other association techniques on male subjects under drug and no-drug conditions. In addition to demonstrated "drug-sensitive" questions, the final form of the inventory (550 "true-false" items) also contains items which may delineate to some extent schizoid and "psychopathic" characteristics. The format is similar to that of the MMPI and the content has a fairly wide range. Initial use indicates that the inventory is effective in differentiating various subjective effects of drugs and in discriminating some

similarities and differences of naturally occurring and experimentally induced behavioral abnormalities. Results also indicate that the effectiveness of specially designed tests, whether in the form of complete sentences or adjective check lists, chiefly depends upon assessment of the "activity-sedation" continuum and allied changes in motivation, alterations in mood such as in a "euphoria-dysporic" continuum, alterations in sensation and perception, and in reportable physiological processes.

268. Hill, H.E., Haertzen, C.A., Wolbach, A.B., and Miner, E.J.: The Addiction Research Center inventory: Appendix. I. Items comprising empirical scales for seven drugs. II. Items which do not differentiate placebo from any drug condition. *Psychopharmacologia* 4:184–205 (1963).

The present listing of items of the Addiction Research Center Inventory (ARCI) is presented as an appendix to papers that describe the development and initial use of this instrument which was devised for assessing subjective effects of drugs. All items are classified according to their effectiveness in discriminating various drug effects from the placebo condition. The drugs used were morphine, amphetamine, pentobarbital, alcohol, LSD–25, pyrahexyl, and chlorpromazine. Two types of scales, developed for each of these conditions separately are presented for each drug under the following headings: 1. Significant scales, composed of items that maintained discrimination at the 0.05 level in two groups of 50 subjects each; 2. Marginally significant scales, composed of additional items for which $P=0.05$ or less in the total sample of 100 Ss; 3. Nondifferentiating items that did not discriminate between placebo and any of the drugs reported upon here. Inspection of these items, answers to which were not changed by drugs, shows a rather striking difference from the "scale-items." When the former are classified for content it is seen that questions concerning attitudes toward individuals and institutions, and questions on philosophy of life including hostilities of various sorts are not generally in the significantly altered category. In contrast, items that are sensitive to drug effects are very frequently questions on sensations, perception, bodily symptoms, moods, drives, attitudes toward taking the test, and motivations. With regard to future work, some anticipated analyses were mentioned in the previous paper which will involve the study of "pattern effects" and other procedures for isolating specificity as well as generality of drug actions.

269. Hill, H.E., Haertzen, C.A., Wolbach, A.B., and Miner, E.J.: The Addiction Research Center Inventory: Standardization of scales which evaluate subjective effects of morphine, amphetamine, pentobar-

bital, alcohol, LSD–25, pyrahexyl and chlorpromazine. *Psychopharmacologia* 4:167–183 (1963).

The ARCI, a 550-item inventory for assessing subjective drug effects and personality characteristics, was standardized using former addict subjects on a number of drug conditions. The inventory was administered under "no-drug" and placebo, and various doses of morphine, pentobarbital, chlorpromazine, LSD–25, amphetamine, pyrahexyl, and alcohol. By means of item analysis, cross-validity, and other initial comparisons, items were chosen to comprise each drug scale that discriminated the particular drug from placebo; the no-drug-placebo comparison also produced a tentative placebo scale. Since nonsignificant differences were found when scoring each of the drug scales separately on the no-drug and placebo conditions, these data were combined for standardizing all scales. Validity generalization, dose-effect, and retest studies showed that the drug scales possessed a high degree of validity and reliability. In contrast, the placebo scale lost discrimination entirely in the validity generalization group. Because of the very considerable number of items comprising the scales, only examples were presented. Subjective effects of the various drugs were discussed in terms of specific and general, nonspecific actions and patterns of these alterations.

270. Isbell, H.: Clinical research on addiction in the United States. In: Livingston, R.B. (ed). *Narcotic Drug Addiction Problems.* Washington, D.C.: U.S. Department of Health, Education, and Welfare, Public Health Service Publication No. 1050, Government Printing Office, 1963.

In reviewing our material, a number of reasonable distinct periods in the history of clinical research in addiction can be defined. In the latter half of the 19th century, the condition was recognized and partially described. Between 1900 and 1920 it became more generally recognized that addiction was partly a medical problem. This period was characterized by speculation as to the "cause" of the disease, with toxic theories dominating clinical thinking and by the development of numerous well-intentioned but useless methods of withdrawal. In the early twenties, the great importance of psychiatric factors was stressed by Kolb. During the late twenties and early thirties, the first clinical research of an experimental sort was begun, culminating in the broad pharmacological, physiological, and psychological program carried on by the Public Health Service until the present time. Despite the enormous effort and the great mass of data which have been gathered, neither laboratory nor clinical research has yielded a simple solution in the problem of drug addiction. Only a very optimistic person would predict that such a solution will soon be forthcoming. Continued efforts

along all lines of research are needed, for there are still great gaps in our knowledge. We do not actually know the entire natural history of drug addiction in our culture. Why is the age distribution of addicts similar in age distribution of either kinds of offenders? What happens to addicts after the age of 35? Though it has been shown that physical dependence has a real physiological basis, the biochemical changes that must mediate the physiological alterations are unknown. Perhaps, the most important of all is our ignorance concerning those conditions classified as personality or character disorders in the Standard Nomenclature of Disease. A greater understanding of these conditions and some method of treatment or prevention, which is practicable and applicable on a mass scale, might go far in solving drug addiction, and many other problems as well.

271. ISBELL, H.: Historical development of attitudes toward opiate addiction in the United States. In: Farber, S.M. and Wilson, R.H.L. (ed.): *Conflict and Creativity.* pp. 54–170. New York: McGraw-Hill, 1963.

This article attempts to trace the historical origins of ambivalent attitudes towards opiate addiction in the United States. On one hand, the addict is regarded as a sick person in need of treatment and on the other as a dangerous criminal who should be incarcerated. The view that the addict is a sick person traces to development of addiction as a result of treatment, or self-treatment, of disease with opiates. The view that addiction is a dangerous vice leading to criminality is traced to the introduction of opium smoking in the United States following importation of Chinese laborers into the West Coast in the latter part of the 19th century which caused opium smoking to be tinged with racial prejudice. This is reinforced by the fact that many addicts are basically antisocial delinquent individuals leading the public to believe that opiates cause crime directly. Confusion of the effects of cocaine with those of opiates tended to cement this view. Around 1920 disgust on the part of the medical profession with physicians who prescribed narcotics for addicts merely for profit and disgust with the clinics that dispensed drugs to addicts helped to crystalize attitudes towards addiction.

272. ISBELL, H.: Need for research on methods of treatment of narcotic addiction. In: Proceedings White House Conference on Narcotic and Drug Abuse. Washington, D.C.: U.S. Government Printing Office, 1963.

All new suggested programs for opiate addiction should be evaluated by rigidly controlled clinical trials. Such trials should be limited in numbers of patients and in time. Application of new programs should not be massive unless the controlled clinical trials are successful.

273. ISBELL, H.: Research on addiction and drug abuse. In: Proceed-

ings White House Conference on Narcotic and Drug Abuse. Washington, D.C.: Government Printing Office, 1963.

Addiction and drug abuse result from a complicated interplay of social, psychological, and pharmacological factors. Continuing basic research in all these fields is necessary for continued progress. A shortage of qualified investigators interested in drug abuse has hampered progress.

274. MARTIN, W.R.: Strong analgesics. In: Root, W.S. and Hofmann, F.G. (ed.): *Physiological Pharmacology* Vol. 1, Part A, pp. 275–305, New York and London: Academic Press, 1963.

Morphine and morphinelike agents seem to have several basic modes of action and the manifold physiological effects that they produce are in part due to their multiple modes of action. A constellation of effects that is invariably associated with analgesia and which has a common basic mode of action has not been defined. All strong analgesics clinically employed are essentially morphinelike, differing only from morphine in such characteristics as rate of onset and duration of action, routes by which they can be administered, potency, analgesic ceiling, and side effects. As understanding of the physiology of pain and suffering is broadened, new screening techniques may be devised that will detect analgesics with modes of action entirely different from morphine.

275. MARTIN, W.R., WIKLER, A., EADES, C.G., and PESCOR, F.T.: Tolerance to and physical dependence on morphine in rats, *Psychopharmacologia* 4:247–260 (1963).

The effects of large doses of morphine in nontolerant and tolerant rats as well as the effects of abruptly withdrawing morphine in rats experimentally addicted to large doses of morphine have been studied on body weight, temperature, metabolic rate, respiratory rate, water consumption, and various forms of motor activity and behavior. In confirmation of many early reports, tolerance develops to certain depressant actions of large doses of morphine and the effects of morphine in the tolerant rat are primarily excitatory, consisting of an increase in body temperature, metabolic rate, and motor activity. The abstinence syndrome of rats addicted to large doses of morphine seems to have two phases: (1) An early phase, which has been called "primary abstinence," consists of weight loss, an increased number of "wet dog" shakes, increased activity, and a fall in body temperature and metabolic rate. The primary abstinence syndrome becomes clearly manifest within 8 to 16 hours following the last dose of morphine and persists for approximately 72 hours. (2) The secondary abstinence syndrome emerges thereafter and consists of a rapid gain in body weight, elevated body temperature and metabolic rate, and an increase in water consumption.

The secondary abstinence syndrome is protracted and small differences have been seen between addicted and control animals as long as 4 to 6 months after withdrawal of morphine.

276. O'Donnell, J.A.: Posthospital study of Kentucky addicts—a preliminary report. *Journal of the Kentucky State Medical Association* 61:573–577 (1963)

277. Rosenberg, D.E., Isbell, H. and Miner, E.J.: Comparison of a placebo, N-dimethyltryptamine and 6-hydroxy-N-dimethyltryptamine in man. *Psychopharmacologia* 4:39–42 (1963).

Five human subjects received intramuscularly at weekly intervals placebo and equal doses of 6-hydroxy-N-dimethyltryptamine (6–HDMT) and N-dimethyltryptamine (DMT) (1 mg/kg, four subjects; 0.75 mg/kg, one subject). DMT produced markedly significant mental effects including anxiety, hallucinations, and perceptual distortions and autonomic changes consisting of pupillary dilation, increase in systolic and diastolic blood pressure, and a decrease in the knee-jerk threshold. These effects appeared within 15–30 minutes and subsided within 1–2 hours. The effects of 6–HDMT were not significantly different from those produced by a placebo.

278. Rosenberg, D.E., Wolbach, A.B., Miner, E.J., and Isbell, H.: Observations on direct and cross tolerance with LSD and *d*-amphetamine in man. *Psychopharmacologia* 5:1–15 (1963).

Within the limits of this experimental design in man: the spectrum of LSD effects is different from that of D-amphetamine in single doses to nontolerant subjects; following the daily administration of LSD for 14 days, direct tolerance develops to LSD (1.5 μg/kg) with respect to pupillary dilatation and mental excitation; following the daily administration of D-amphetamine for 14 days, direct tolerance develops to D-amphetamine (0.6 mg/kg) with respect to temperature elevation, systolic blood pressure increase, and mental excitation; subjects directly tolerant to LSD (1.5 μg/kg) are not cross-tolerant to D-amphetamine (0.6 mg/kg), and subjects directly tolerant to D-amphetamine (0.6 mg/kg) are not cross-tolerant to LSD (0.5 μg/kg). It is inferred that LSD and D-amphetamine probably exert their effects through dissimilar mechanisms.

279. Sloan, J.W., Brooks, J.W., Eisenman, A.J., and Martin, W.R.: The effect of addiction to and abstinence from morphine on rat tissue catecholamine and serotonin levels. *Psychopharmacologia* 4:261–270 (1963).

Four groups of 24 Wistar strain albino rats, equally divided as to sex,

were injected subcutaneously twice daily with morphine sulfate on a rapidly increasing dosage schedule (5 mg/kg/day to a maximum of 160, 260, or 400 mg/kg/day) over a period of about 40 days, along with 12 saline-treated controls for each group. One group (maximum of 400 mg of morphine sulfate/kg/day) was sacrificed about 2 hours after the last injection of morphine, to reflect the effects of addiction. Addicted animals failed to gain weight as rapidly as saline-treated controls and had very little body fat. Morphine addiction did not alter brain weights, but it did significantly decrease heart weights. The spleens tended to weigh less than controls, though not significantly so, while the adrenal glands were hypertrophied. Brain catecholamine levels showed a statistically significant increase over saline controls, but serotonin levels were unchanged. Heart and splenic catecholamines, both on the basis of concentration and total content, tended to decrease, though the changes were not statistically significant. Splenic serotonin, in terms of either concentration or content, was significantly elevated during addiction. The other three groups of animals (maximum of 160, 260, or 400 mg of morphine sulfate/kg/day) were sacrificed at 24 or 48 hours after the last injection, to reflect the effects of abstinence. The rats lost weight during withdrawal and had very little body fat when sacrificed. Brain weights were unchanged, heart and splenic weights showed a statistically significant decrease, and the adrenal glands were significantly hypertrophied. Brain catecholamines returned to normal and brain serotonin was unchanged. Heart catecholamines, either on the basis of concentration or content, were significantly depressed as a consequence of abstinence. Splenic catecholamines and serotonin were significantly increased in terms of concentration, but the total amounts returned to, or remained normal.

280. Wikler, A.: Psychologic bases of drug abuse. In: Proceedings White House Conference on Narcotic and Drug Abuse. Washington, D.C.: U.S. Government Printing Office, 1963.

281. Wikler, A., Martin, W.R., Pescor, F.T., and Eades, C.G.: Factors regulating oral consumption of an opioid (etonitazene) by morphine-addicted rats. *Psychopharmacologia* 5:55–76 (1963).

Rats made partially tolerant to, and then maintained on single daily intraperitoneal injection of morphine, 200 mg/kg, each morning (E's), and normal rats similarly injected with saline (C's) were compared with regard to volumes of and rates at which (cumulative lap counts) water or very dilute aqueous solutions of etonitazene were consumed without prior water-deprivation during the first 7 and succeeding 17 hours after the morning injections each day, and with regard to the effects of such drinking on "activity" scores, "wet dog" frequencies, oxygen consump-

tion rates, and colonic temperatures. Total 24-hour intake of water was not significantly different, but the largest part was consumed by C's during the second (17 hour) period and by E's in the first (7 hour) period, water-drinking in the latter slowing abruptly about 13–14 hours after the morning injection of morphine, when the earliest signs of abstinence became manifest. In C's the temporal pattern of drinking was not altered by substitution of 5 or 10 μg/ml aqueous solutions of etonitazene for water, nor were the 24-hour intakes of the two fluids significantly different. In E's no change in volumes consumed occurred when such substitution was made during the first (7 hour) period after the morning injection of morphine, but when the substitution was made during the second (17 hour) period, volumes of etonitazene solution consumed were very much greater than when E's or C's were drinking water. However, when the concentration of etonitazene was raised to 20 or 40 μg/ml, the volumes consumed by E's during the second (17 hour) period, while still exceeding intake of water by these animals, were not significantly different from those of C's drinking water during the same period. Whereas C's drank a 5 μg/ml aqueous solution of etonitazene at about the same rate as they drank water during the second (17-hour) period, a marked acceleration of rate of drinking was displayed by E's beginning about 17–18 hours after the morning injection of morphine, when this concentration of etonitazene was substituted for water during the same period. After drinking etonitazene solution for 17 hours in any of the concentrations employed, E's did not display increased "wet dog" frequencies and hypothermia (preinjection morphine-abstinence phenomena). However, complete "normalization" was achieved only after drinking the 10 or 20 μg/ml concentrations, hypoactivity being observed when the concentration was 5 μg/ml and increased oxygen consumption rates and hyperthermia being found when the concentration of etonitazene was 40 μg/ml. In C's or in E's the effects of single doses of etonitazene were qualitatively similar to those of morphine when these drugs were injected intraperitoneally, and in E's "permanent" substitution of etonitazene for morphine intraperitoneally resulted in a syndrome of chronic intoxication similar to that produced by morphine (increased "activity," oxygen consumption rates and colonic temperatures). Likewise, abrupt withdrawal of etonitazene resulted in the appearance of succeeding "primary" and "secondary" abstinence syndromes similar to those of morphine, though at least at the chronic daily dose levels compared (morphine 200 mg/kg and etonitazene 300 μg/kg i.p.), the early (24 to 27 hours abstinent) etonitazene abstinence syndrome appeared to be less intense than that of morphine. It is concluded that suppression of abstinence phenomena is the major factor regulating oral consumption of etonitazene in dilute aqueous solutions by morphine-addicted rats and that the pharmacological properties

of etonitazene and morphine are sufficiently similar to warrant use of etonitazene solutions in lieu of morphine solution as an oral reinforcing agent in studies on conditioning of opioid-acquisitory behavior in this species.

282. Wikler, A. and Pescor, F.T.: Further studies on the use of etonitazene (I–G–2) in drinking water as a reinforcing agent in conditioning of opioid drug-seeking behavior in rats. *Committee on Drug Addiction and Narcotics,* Washington, D.C.: National Academy of Sciences, National Research Council, 1963.

From the technical standpoint, the studies described in this report have demonstrated both the feasibility of using etonitazene in drinking water as a reinforcing agent in conditioning of drug-seeking behavior in animals, and certain aversive properties of this drug for rats, the basis of which is as yet unclear. Also, the studies have shown that anise-flavor can serve very well as a discriminative cue, being "neutral" or mildly aversive *per se* for rats. In addition, comparison of the results obtained in studies A and B with those in E indicate that use of extreme degrees of water-deprivation for motivating rats to drink at times convenient for the experimenter introduces a complicating variable, the effects of which on the results obtained are difficult to interpret. From the theoretical standpoint, the data obtained in Study E, interpreted in the light of the findings in Studies C and D, lend support to the concept that "relapse" is due at least in part to conditioning factors operating during previous episodes of "physical dependence" on morphinelike drugs. This formulation is not meant to exclude previous episodes of morphine-"euphoria" as contributory factors in subsequent relapse (though the senior author feels this factor has been greatly over stressed in the literature), but rather to focus attention on the contribution made by "physical dependence," both through classical conditioning of this process and through the opportunities it affords for repeated reinforcement of instrumental (opioid-acquisitory) behavior. In the latter respect, the conclusions reached by the present authors are in agreement with those of other investigators who used quite different methods. Finally, some speculations may be offered about the significance of the findings in these studies for clinical practice. If the conclusions reached about the factors contributing to "relapse" in rats apply also to man, then the drug-withdrawal phase in the treatment of narcotic addicts assumes a degree of importance much greater than that hitherto assigned to it. For the most part, research in this area has been devoted to finding "painless" methods of withdrawal. While eminently justifiable on practical and humanitarian grounds, such methods alone do not promote "extinction" of the postulated classical conditioning or instrumental reinforcing factors discussed above. If an analogy may be made with food-reward

motivated bar-pressing behavior in hungry animals, then gradual or rapid withdrawal of morphine or heroin, or substitution of and subsequent withdrawal of methadone in human addicts are functionally equivalent to "satiation"—i.e., "drive-removal" by feeding, instead of true "extinction" by nonreinforcement. As is well known, bar-pressing rates of food-satiated rats will drop sharply, but the bar-pressing "habit" is manifested promptly in full force when the animal is made hungry again. Similarly, addicts withdrawn by present methods may show no drug-acquisitory behavior after subsidence of "unconditioned" morphine or heroin abstinence phenomena as long as they are in "home cages" (drug-free institutional environments) but their "hustling" habits are likely to become manifest again when they are transferred to the "mazes" of Harlem, or other environments with high drug availability, which serve to evoke "conditioned abstinence" phenomena. If these speculations are valid, then one of the most important tasks for future research is the development of methods of narcotic drug withdrawal which are at once both humane and effective for true extinction of "conditioned abstinence" and of reinforced drug-seeking behavior.

283. Wolbach, A.B. and Fraser, H.F.: Addiction liability of I–C–26 (dextro-3-dimethyl-amino-1,1-diphenylbutyl ethyl sulfone hydrochloride) and I–D–20 (ethyl 1-(2-carbamethyl)-4-phenylpiperidine-4-carboxylate hydrochloride). *Bulletin on Narcotics* 15:25–26 (1963).

Ethyl 1-(2-carbamylethyl)-4-phenylpiperidine-4-carboxylate hydrochloride (I–D–20) in single oral doses of 180 or 1,000 mg induces an incomplete morphinelike pattern of response which varies from subject to subject, even with doses of 1,000 mg. Administration of the drug subcutaneously produces no increased response over the oral route in dosages of 20 mg to 175 mg. Orally, 4,500 mg of I–D–20 in 24 hours suppressed symptoms of abstinence from morphine only partially. One convulsion occurred in one patient receiving this dose of the drug. It is therefore concluded that the addiction liability of I–D–20 is low.

1964

284. Ball, J.C.: Drug diagnosis of 3,301 addict patients at Lexington and Ft. Worth hospitals. Presented to Committee on Drug Addiction and Narcotics, National Research Council, National Academy of Sciences (1964).

285. Bates, W.: Treating narcotic addicts. *The Reign* 36:22–66 (1964).

286. Chessick, R.D., Haertzen, C.A., and Wikler, A.: Tolerance to LSD–25 in schizophrenic subjects. Attenuation of effects on pupillary diameter and kneejerk threshold after chronic intoxication. *Archives of General Psychiatry* 10:653–658 (1964).

In 10 chronic schizophrenic patients, single oral doses of LSD–25 (1.0 μg, 1.5 μg, and 3.0 μg/kg) each produced degrees of pupillary dilatation and lowering of knee-jerk thresholds that were significantly different from the effects of placebo. The pupillary response to 1.5 μg/kg was significantly greater than to 1.0 μg/kg, but equal to 3.0 μg/kg of the drug. The effect of 3.0 μg/kg of LSD–25 on knee-jerk threshold was greater than that of either 1.5 μg or 1.0 μg/kg, but these two doses produced effects that were not significantly different from each other.

In studies completed on nine of the chronic schizophrenic subjects, the effects of LSD–25, 1.5 μg/kg, on both pupillary diameter and knee-jerk thresholds were significantly attenuated after 6 days of once-daily treatment with the drug, in doses increasing by daily increments of 0.25 μg/kg from 0.25 μg/kg on the first, to 1.5 μg/kg on the sixth day, indicating that as in nonpsychotic subjects, tolerance to LSD–25 can be acquired by chronic schizophrenic patients.

The effects of LSD–25 (1.5 μg/kg) on knee-jerk thresholds in the chronic schizophrenic patients were comparable to those observed in a concurrent study on nonpsychotic postaddict subjects, but the pupillary effects appeared to be smaller in the schizophrenic patients. Some evidence is presented that this apparent difference may be related to the greater mean age of the schizophrenic, as compared with the postaddict group, and that regardless of this dichotomous nosologic classification, the effects of LSD–25 on pupillary response (but not on knee-jerk threshold) may be negatively correlated with age.

287. Essig, C.F.: Addiction to nonbarbiturate sedative and tranquilizing drugs. *Clinical Pharmacology and Therapeutics* 5:334–343 (1964).

Increasing numbers of nonbarbiturate sedative drugs are being introduced into medical practice. Despite their nonbarbiturate chemical structure and regardless of designations other than "sedative-hypnotic," at least six of the newer depressant drugs can cause states of intoxication and physical dependence that are clinically similar to those induced by barbiturates. These drugs are meprobamate (Miltown, Equanil), glutethimide (Doriden), ethinamate (Valmid), ethchlorvynol (Placidyl), methyprylon (Noludar), and chlordiazepoxide (Librium). The behavioral effects of these drugs and their combination with ethanol may become an increasingly important public hazard. The abstinence syndromes that can result from the abrupt withdrawal of excess dosages of these drugs include convulsions and psychotic behavior. Death has been attributed to withdrawal of meprobamate and methyprylon. Office or

ambulatory withdrawal of any of these drugs after use in large dosage is not recommended. Gradual dosage reduction or barbiturate substitution prior to its gradual withdrawal during hospitalization is suggested. Substitution of diphenylhydantoin (Dilantin) or any of the phenothiazines as the sole means of support during sedative-hypnotic drug withdrawal is a questionable practice.

288. Essig, C.F.: Barbiturate withdrawal convulsions in decerebellate dogs. *International Journal of Neuropsychiatry* 3:453–456 (1964).

In order to assess the role of the cerebellum in mechanisms underlying barbiturate withdrawal convulsions, this structure was ablated in a series of 19 dogs prior to intoxicating them to various chronic dose levels of sodium barbital. Nine such preparations and 10 intact dogs survived to undergo barbiturate withdrawal. During the first addiction and withdrawal cycle two decerebellate and four intact dogs developed abstinence convulsions. Decerebellation did not seem to increase or decrease the tendency to develop abstinence convulsions when all final dosage levels of barbital were considered. Cerebellar ablation did not affect the number or duration of the abstinence convulsions that developed. It is concluded that the cerebellum is not a requisite site of origin for such seizures nor a necessary substrate for their development or sustainment.

289. Essig, C.F. and Flanary, H.G.: Repeated electroconvulsions: elevation of threshold proximal and distal to origin. *Experimental Neurology* 9:31–35 (1964).

The daily induction of generalized tonic-clonic convulsions by means of electrical stimulation across the cerebral hemispheres in cats results in a gradual increase in the electroconvulsive threshold (ECT). It has now been shown that the ECT elevation is not confined to the site of the electrodes used for daily stimulation. In four cats extra electrodes were placed 2.2 to 3.0 cm distal to those used for the daily induction of convulsions during 8 to 14 days. After the ECT had increased proximally it was also found to be significantly elevated distally. It is postulated that the tolerancelike ECT elevation is due to a generalized functional adaptation in the brain which may have a chemical basis.

290. Fraser, H.F., Jones, B.E., Rosenberg, D.E., and Thompson, A.K.: Effect of a cycle of addiction to intravenous heroin on certain physiological measurements. *Bulletin on Narcotics* 16:17–23 (1964).

Selected physiological measurements were determined on five former heroin addicts while receiving an intravenous placebo for 28 days. These subjects were then addicted for 61 days to intravenous heroin HCl and the observations repeated. The average initial daily dose of heroin was 10 mg; this was increased to an average of 96 mg on the

18th day of addiction and maintained at that level for 43 additional days. The experimental design was double blind (a parallel experiment was carried out on five other subjects and certain measurements in this study, not previously reported, are included herein). In four of the five subjects, heroin as compared with a placebo depressed physical activity as indicated by increased hours of sleep, increased hours lying horizontal in bed, and reduced hours off the research ward daily. Heroin provoked repeated episodes of vomiting and a loss of weight in all subjects. The incidence of "nodding" (observations for closed eyelids while subjects were viewing a television program) was increased in four of the five subjects while receiving heroin. Overall the health of the subjects was satisfactory throughout this experimental period. Performance of a coding test which required close attention for an average of 12 minutes showed no impairment during addiction. During addiction the subjects showed an improvement in performance upon introduction of a mild incentive (timing the test).

After 61 days of chronic intoxication with heroin a sharp reduction of the dosage of heroin was followed by quite severe signs of abstinence which promptly declined after heroin was again administered. The abstinence syndrome resembled that observed after withdrawal of morphine. In 8 of 10 subjects (utilizing data from both experiments) heroin as compared to a placebo significantly depressed respiratory rate, and in 8 of the 10 subjects, rectal temperature was significantly increased. The effect on systolic blood pressure varied among the 10 subjects but the average effect was nil.

291. Fraser, H.F. and Rosenberg, D.E.: Studies on the human addiction liability of 2′-hydroxy-5,9-dimethyl-2-(3,3-dimethylallyl)-6,7-benzomorphan (Win 20,228): a weak narcotic antagonist. Presented to Committee on Drug Addiction and Narcotics, National Research Council, National Academy of Sciences, 1963. *The Journal of Pharmacology and Experimental Therapeutics* 143:149–156 (1964).

2′-Hydroxy-5,9-dimethyl-2-(3,3-dimethylallyl)-6,7-benzomorphan (Win 20,228) has been evaluated for addictiveness in former opiate addicts. In crossover designed experiments Win 20,228 was compared with morphine, placebo, and *d*-propoxyphene in one test. In single subcutaneous doses the effects of Win 20,228 were subjectively different from morphine and less frequently identified as an opiate.

Single intravenous doses of Win 20,228 (35 mg/70 kg) showed significantly less morphinelike effects than intravenous morphine (25 mg/70 kg); and less opiate effects than *d*-propoxyphene (160 mg/70 kg). Win 20,228 was substituted for morphine in morphine-dependent subjects using the maximum tolerated and/or accepted dosage. Addicts did

not like the effects induced and there was no significant suppression of abstinence signs.

Chronic administration of Win 20,228 was disliked by opiate addicts. Seven of eight subjects elected to stop taking it, whereas none discontinued morphine. The eighth subject (who continued on Win 20,228 for 25 days despite a severe inflammatory reaction at injection sites) showed a mild but definite abstinence syndrome when the drug was discontinued, but no physical dependence was demonstrated by the nalorphine test. On the other hand, when morphine was chronically administered, its effects were consistently liked by all these subjects. Definite physical dependence was demonstrated by the nalorphine test, and when morphine was abruptly withdrawn the intensity of abstinence observed was much greater than that following withdrawal of Win 20,228.

It is concluded from these experiments that Win 20,228 has definitely less addictiveness (abuse liability) than morphine and, insofar as the experiments may be interpreted, the degree of addictiveness approximates that of *d*-propoxyphene.

292. Gorodetzky, C.W. and Isbell, H.: A comparison of 2,3-dihydro-lysergic acid diethylamide with LSD–25. *Psychopharmacologia* 6:229–233 (1964).

The 2,3-dihydro-diethylamide of lysergic acid induces LSD-like autonomic and mental changes in man but is less potent than LSD. The effects of 2,3-DH-LSD appear more slowly than those of LSD–25. The low potency (relative to LSD–25) of 2,3-DH-LSD in inducing fever in rabbits correlates with a relatively low potency in inducing autonomic and psychotomimetic effects in man.

293. Haertzen, C.A.: On the Addiction Research Center Inventory. Scores of former addicts receiving LSD and untreated schizophrenics. *Psychological Reports* 14:483–488 (1964).

Thirteen untreated male schizophrenics were compared with more than 150 postaddicts under three conditions: no-drug, placebo, and 1.5 μg/kg of LSD–25, using two LSD scales. On an LSD scale that is sensitive to more general drug effects schizophrenics were differentiated from addicts under a no-drug condition, but they were not differentiated from addicts who were given LSD. However, on a more specific LSD scale, addicts under LSD were differentiated from untreated schizophrenics as well as addicts under no-drug, placebo, and six other drugs. It appears that there are similarities and differences between responses of schizophrenics and postaddicts to LSD.

294. Isbell, H., Rosenberg, D.E., Miner, E.J., and Logan, C.R.: Tolerance and cross tolerance to scopolamine, N-ethyl-3-piperidyl-

benzylate (JB–318) and LSD–25. In: Bradley, P.B., Flugel, F., and Hoch, P.H. (eds.): *Neuropsychopharmacology,* Vol. 3, pp. 440–448. New York/ Amsterdam/London: Elsevier Publishing Company, 1964.

Patients treated chronically with LSD, scopolamine, and N-ethyl-3-piperidyl benzylate (JB–318) for 3 weeks became tolerant to the mental and some of the autonomic effects of these drugs. Patients tolerant to the two cholinergic blockers showed a prolonged mental reaction to LSD. Patients tolerant to LSD showed a decrease in the number of symptoms after the cholinergic blockers. There was evidence both for and against cross-tolerance between scopolamine and JB–318. The experiments must be extended to a larger number of patients.

295. Martin, W.R. and Eades, C.G.: A comparison between acute and chronic physical dependence in the chronic spinal dog. *The Journal of Pharmacology and Experimental Therapeutics* 146:385–394 (1964).

Experiments aimed at comparing acute and chronic tolerance to, as well as acute and chronic physical dependence on, morphine were conducted in both high (C5–C6) and low (T–10) chronic spinal dogs. Abstinence signs, precipitated by nalorphine, originating in both supraspinal portions of the nervous system as well as in spinal cord structures below the level of transection were studied. Acute physical dependence develops in the spinal cord; however, both acute tolerance and acute physical dependence develop more rapidly and more completely in supraspinal structures. The spinal cord has a capacity equal to or greater than that of supraspinal structures to develop chronic tolerance and physical dependence. These findings indicate that acute and chronic tolerance as well as acute and chronic physical dependence are, to an extent, qualitatively different and suggest there may be several mechanisms involved in the development of tolerance to and physical dependence on morphine. A part of the precipitated abstinence syndrome in the acutely physically dependent dog can be explained on the basis of a "homeostatic resensitization hypothesis." However, spinal cord signs of precipitated abstinence in the acutely physically dependent dog cannot be explained by this hypothesis.

296. Martin, W.R., Eades, C.G., Fraser, H.F., and Wikler, A.: Use of hindlimb reflexes of the chronic spinal dog for comparing analgesics. *The Journal of Pharmacology and Experimental Therapeutics* 144:8–11 (1964).

A method using the hindlimb reflexes of chronic spinal dogs for determining the relative potency of morphine, codeine, and I–K–1, which is reproducible and sensitive has been described. Since the actions of the drugs upon effector systems innervated by portions of the nervous system above and below the level of transection can be easily

studied together, a qualitative and quantitative assessment of the drugs' actions can be made.

297. Martin, W.R., Fraser, H.F., Gorodetzky, C.W., and Rosenberg, D.E.: Additional studies on the addictiveness of 2-cyclopropylmethyl-2'-hydroxy-5,9-dimethyl-6,7-benzomorphan (Win 20,740; ARC II–C–3). Presented to Committee on Drug Addiction and Narcotics, National Research Council, National Academy of Sciences, 1964.

298. Mulé, S.J.: Determination of narcotic analgesics in human biological materials. Application of ultraviolet spectrophotometry, thin layer and gas liquid chromatography. *Analytical Chemistry* 36:1907–1914 (1964).

The rapid quantitative extraction of narcotic analgesics from human biological material and the analysis of each extract by ultraviolet spectrophotometry, thin-layer chromatography, and gas-liquid chromatography is described. Maximum and minimum absorbance values as well as molar absorptivity data were determined in 0.1N HCl, 0.2N NaOH, absolute ethanol, and 25 percent isobutanol in ethylene dichloride. The bathochromic shift in alkali was not observed when the free phenolic hydroxyl of the analgesic drug was altered. Thin layer chromatographic (silica gel G and buffered, pH 8.0, cellulose powder adsorbent) R_f values of the drugs were determined in seven different solvent systems. Gas-liquid chromatographic retention data were obtained for the free drug base as well as the acetylated and propionated column derivatives on a 2 percent SE–30 siloxane polymer column at 215° C. Unique differences were observed between 31 compounds in five different chemical families. Usually 3 to 5 hours were required to extract and completely analyze a biological sample for the presence of microgram quantities of narcotic analgesics.

299. Mulé, S.J.: Rapid determination of narcotic analgesics in human biological fluids and tissues. Application of gas-liquid chromatography, thin-layer chromatography, and UV spectrophotometry. Presented to Committee on Drug Addiction and Narcotics, National Research Council, National Academy of Sciences, 1964.

300. O'Donnell, J.A.: A follow-up of narcotic addicts: mortality, relapse and abstinence. Presented to Committee on Drug Addiction and Narcotics, National Research Council, National Academy of Sciences, 1964.

301. Rosenberg, D.E., Isbell, H., Miner, E.J., and Logan, C.R.: The

effect of N, N-dimethyltryptamine in human subjects tolerant to lysergic acid diethylamide. *Psychopharmacologia* 5:217–227 (1964).

The spectrum of effects produced with single doses of N,N-dimethyltryptamine (DMT) in six nontolerant human subjects resembled those produced with lysergic acid diethylamide (LSD). Either drug produced an elevation in systolic blood pressure, a decrease in the threshold for the knee jerk, pupillary dilation, and a mental response characterized by anxiety, perceptual distortions, and hallucinations. The onset and duration of action was shorter with DMT (0.5 mg/kg) as compared to LSD (1.5 μg/kg), but the maximum intensity of effects with respect to each parameter was equivalent for both drugs. Following the chronic administration of LSD only a mild degree of cross-tolerance to the mental response could be demonstrated with DMT (0.5 mg/kg) in subjects highly tolerant to the pupillary, knee jerk, and mental effects of LSD (3.0 μg/kg). It is inferred that the site or mechanism which is altered during LSD tolerance is not one which is primarily concerned with the action of DMT.

302. Wikler, A.: Survey of research on alcohol. Proceedings of 26th International Congress on Alcohol and Alcoholism, 7/31–8/5/60, pp. 57–65. Stockholm: Eklunds & Vasatryck, 1964.

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303. Ball, J.C.: Book review: Cressey, D.R. *Delinquency, Crime and Differential Association.* The Hague: Martinus Nijhoff, 1964. *Social Forces* 43:614 (1965).

304. Ball, J.C.: Two patterns of narcotic drug addiction in the United States. *Journal of Criminal Law, Criminology and Police Science* 56:203–211 (1965).

Analysis of the medical records of 3,301 addict patients discharged from the Lexington and Fort Worth Hospitals in 1962 reveals that two quite distinct patterns of opiate addiction exist in the United States. One pattern of addiction consists of heroin use among metropolitan youth who came predominantly from the minority groups in American society. The other pattern of addiction consists primarily of middle-aged whites who use opiates other than heroin or synthetic analgesics; this second pattern of addiction is concentrated in the Southern States. A comparison of the addict patients at the two hospitals in 1962 with the 1937 hospital population described by Pescor reveals that marked changes have occurred during this 25-year period. The male patients

are younger by some 8 years. The use of heroin prior to admission has increased, while the use of morphine has decreased. The proportion of the patients who came from northern metropolitan centers has increased notably; still, high rates of hospitalization have continued from many of the Southern States. Thus, the major change has been the increasing preponderance of heroin addicts from the minority groups of our largest cities.

305. Ball, J.C. and Cottrell, E.S.: Admissions of narcotic drug addicts to Public Health Service Hospitals, 1935–63. *Public Health Reports* 80:471–475 (1965).

From 1935 through 1963 there were 84,625 addict admissions to the U.S. Public Health Service hospitals at Lexington, Ky., and Fort Worth, Tex. The number of addict admissions to the two hospitals reached a peak of 4,533 in 1950. Since that year, there has been a general decline in the yearly number of admissions; there were 3,111 addict admissions during 1963. When addict patients admitted in 1937 were compared with those admitted in 1963, the 1963 hospital population was found to be younger, to come more frequently from the largest metropolitan areas, and was more likely to be nonwhite than addicts admitted for treatment in 1937.

306. Essig, C.F.: Clinical aspects of barbiturates and sedative drug abuse. *American Journal of Hospital Pharmacy* 22:140–143 (1965).

When taken chronically in doses exceeding usual therapeutic amounts meprobamate, glutethimide, ethinamate, ethchlorvynol, methyprylon, and chlordiazepoxide have been reported to cause states of intoxication and/or physical dependence, either of which might be harmful to the user or society. Therefore, like the barbiturates, these are considered to be drugs of addiction. Death has been attributed to the abrupt withdrawal of large doses of barbiturate, meprobamate, and methyprylon.

307. Essig, C.F.: Repeated electroconvulsions resulting in elevation of pentylenetetrazole seizure threshold. *International Journal of Neuropharmacology* 4:201–204 (1965).

The daily induction of generalized tonic-clonic convulsions by means of electrical stimulation across the cerebral hemispheres in cats results in a gradual increase in the electroconvulsive threshold (ECT). In attempting to gain more insight into this tolerancelike phenomenon it was determined that the ECT elevation also resulted in "cross-tolerance" to pentylenetetrazole-induced convulsions. Six cats in which pentylenetetrazol convulsive thresholds (PCT) were determined both before and after a series of electroconvulsions developed PCT elevations

ranging from 6.3 to 165.4 percent. The mean PCT elevation was 86.1 percent and the mean ECT elevation was 142.2 percent. Although both threshold elevations were statistically significant, there was no correlation between the extent of ECT and PCT elevations within cats. It was concluded that some, but not all, of the tolerance mechanisms underlying the ECT and PCT elevations were the same. The nature of these mechanisms remains to be determined.

308. Gorodetzky, C.W. and Martin, W.R.: A comparison of fentanyl, droperidol and morphine. *Committee on Problems of Drug Dependence.* Washington, D.C.: National Academy of Sciences, National Research Council, 1965. *Clinical Pharmacology and Therapeutics* 6:731–739 (1965).

Single intramuscular doses of fentanyl, droperidol, fentanyl plus droperidol, morphine, and placebo were compared in a double blind, crossover study on six normal male postnarcotic addicts. Miotic effects were assessed by pupillography, opiate signs and symptoms, and liking by questionnaires. Fentanyl alone was found to be similar to morphine in its pattern of signs and symptoms and its high frequency of identification as a narcotic. For equimiotic doses, fentanyl is at least as euphorogenic as morphine. In the combination of fentanyl plus droperidol, droperidol alters some of the morphinelike effects of the mixture, making the mixture similar to droperidol alone. However, if the dose of fentanyl in the mixture is increased, more of its morphinelike effects emerge. For equimiotic doses the combination is not more euphorogenic than morphine or fentanyl alone. The time courses of fentanyl, droperidol, and fentanyl plus droperidol are similar and differ from morphine in their shorter duration of action. All effects of the combination of fentanyl plus droperidol could be accounted for by the additive effects of each drug alone. Therefore, droperidol does not potentiate any of the effects of fentanyl. Extrapyramidal reactions were noted in 7 of 15 subjects who received single intramuscular doses of droperidol alone, and in 1 of 8 subjects who received single intramuscular doses of fentanyl plus droperidol in combination. These reactions were readily relieved by intramuscular administration of benztropine or diphenhydramine.

309. Haertzen, C.A.: Addiction Research Center Inventory (ARCI): Development of a general drug estimation scale. *Journal of Nervous and Mental Disease* 141:300–307 (1965).

A general drug control-estimation scale (DE) was developed for the Addiction Research Center Inventory using 100 opiate addict subjects. Two requirements need to be satisfied for the DE scale. One is that the scale should reflect scores to be expected on empirically derived drug

effect scales for a no-drug condition or it should be resistant to the effects of psychologically active drugs. The other requirement is that the scale should correlate with empirically derived drug effect scales. The scale satisfies both criteria. Consequently, the difference in the score on empirical scales and the DE scale is a reliable index of the presence or absence of drug effects for morphine, amphetamine, pentobarbital, LSD, alcohol, chlorpromazine, and pyrahexyl that were used in the study. The DE score indicates the expected scores on empirical drug scales for a no-drug condition in opiate addicts. The DE scale is the most reliable scale in the Addiction Research Center Inventory using test-retest methods and reliability is not attenuated by drugs. DE is relatively more weighted with items on hostility, low frustration tolerance, inadequacy, and familial problems.

310. Haertzen, C.A.: Subjective drug effects: A factorial representation of subjective drug effects on the Addiction Research Center Inventory. *Journal of Nervous and Mental Disease* 140:280–289 (1965).

Five hundred fifty questions from the Addiction Research Center Inventory were factor analyzed using the responses of 100 postaddict male Ss who were given 1.5 μg/kg of LSD–25. Ten factors were extracted but only two of these were substantially related to the effects of eight drugs: LSD, morphine, amphetamine, pentobarbital, chlorpromazine, pyrahexyl, alcohol, and scopolamine. All drugs in the series produced significant change on the first factor, reactivity. It is theoretically possible that the factor is general enough to be sensitive to other states, such as physical or mental illness, that may contain some general reactive component associated with change. The second factor, efficiency, is a polar factor in the sense that some drugs produce effects on it which are opposite to those under placebo. Thus, amphetamine increased the feeling of energy and memory capacity, but other drugs (such as scopolamine) decrease the feeling. Using these two factors, a general spectrum of similarities and differences among drugs can be demonstrated and serves as an organizing principle for relating subjective drug effects. Thus, the subjective effects of amphetamine are more similar to those of morphine than to those of LSD. The effects of chlorpromazine are more similar to those of alcohol and pentobarbital than to those of amphetamine or morphine. The effects of morphine and amphetamine are opposite to some of the effects of chlorpromazine. Some of the effects of amphetamine are opposite those of alcohol, pentobarbital, LSD, chlorpromazine, and scopolamine. The factor loadings for the first two factors are correlated with the magnitude of certain drug effects. At least part of the pattern of drug effects may be simulated by certain Ss in a nondrug state.

311. Haertzen, C.A. and Miner, E.J.: Effect of alcohol on the Guilford-Zimmerman scales of extroversion. *Journal of Personality and Social Psychology* 1:333–336 (1965).

According to Eysenck's theory depressant drugs should increase extraversion. Eighty postnarcotic addicts were given the Guilford-Zimmerman Temperament Survey under no-drug and alcohol (3.0 cm^3/kg of 30 percent alcohol) conditions. No significant differences were found on scales that measure extraversion-introversion. Lack of significance for the Rhathymia (R) scale was associated with lack of significance for items. The R scale was not significantly correlated with the Addiction Research Center Inventory scales for alcohol or amphetamine. Therefore, no direct confirmation of Eysenck's theory was found. However, it was suggested that some extraversion (R) items as well as items from other scales would be sensitive to effects of drugs if they were rewritten so as to suggest reactivity or current psychological status.

312. Isbell, H.: Perspectives in research on opiate addiction. In: Wilner, D.M. and Kassebaum, G.G. (eds.): *Narcotics,* pp. 36–50. New York McGraw-Hill, Inc., 1965.

Opiate addiction is a very complex process in which pharmacologic, psychologic, biochemical, and socioeconomic factors play interdependent roles. Basic research in each of these fields is necessary. The state of knowledge in each of these fields is reviewed and suggestions for future research are suggested.

313. Jones, B.E.: Visual recognition thresholds for narcotic argot in postaddicts. *Perceptual and Motor Skills* 20:1065–1069 (1965).

Visual recognition thresholds were determined for matched pairs of words. Each pair of words contained one which belonged to the argot of the narcotic addict and one word which did not. Thresholds obtained on 37 hospitalized postaddicts and 19 normals were significantly lower on argot words than on nonargot words for the postaddict group, while the normals showed no significant differences. Supplementary ratings on familiarity of the words showed a significant general relation between recognition thresholds and familiarity. In addition, the postaddicts rated argot words as significantly more familiar than nonargot words.

314. Jones, B.E., Ayers, J.J.B., Flanary, H.G., and Clements, T.H.: Effects of morphine and pentobarbital on conditioned electrodermal responses and basal conductance in man. *Psychopharmacologia* 7:159–174 (1965).

The effects of morphine (8 mg and 16 mg/70 kg) and pentobarbital (200 mg/70 kg) upon acquisition of a conditioned electrodermal re-

sponse were studied. Both morphine (16 mg) and pentobarbital tended to reduce the degree of conditioning. In addition, morphine (16 mg) attenuated the increase in basal conductance relative to that which occurred under placebo during the conditioning period and did so more effectively than pentobarbital. Pentobarbital, but not morphine, decreased basal conductance under the nonshock condition. Morphine thus acted selectively on the effects of shock on basal conductance, and thereby, possibly, on anxiety. Neither morphine nor pentobarbital appeared to impair responsivity of the phasic EDR. The tentative hypothesis was offered that the tonic and phasic reactions of the electrodermogram are separately mediated and that morphine has a greater effect upon the neural basis for the tonic than for the phasic reaction.

315. MARTIN, W.R.: Book review: Chein, I., Gerard, D.L., Lee R.S., and Rosenfield, E. *The Road to H. Narcotics, Delinquency, and Social Policy.* New York: Basic Books, 1964. 482 p. *Journal of Nervous and Mental Disease* 140:471–473 (1965).

316. MARTIN, W.R.: Drug addiction. In: DiPalma, J.R. (ed.): *Drill's Pharmacology in Medicine* (ed. 3), pp. 274–285. New York: McGraw-Hill, 1965.

317. MARTIN, W.R.: Drug addiction. In: *The World Book Encyclopedia,* Vol. D, pp. 288d–289. Chicago, Ill.: Field Enterprises Educational Corp., 1965.

318. MARTIN, W.R.: Some clinical aspects of addiction to narcotic analgesics. *American Journal of Hospital Pharmacy* 22:133–139 (1965).

The abuse liability of any drug, including narcotic analgesics, must be adjudged in several frames of reference for its (a) capacity to induce compulsive drug-seeking behavior, (b) potential for causing toxic changes either when administered in single doses or chronically, and (c) its ability to produce effects that are regarded by our society as undesirable and/or injurious to society and to the individual. There are several types of abnormalities in addition to the changes produced by narcotic analgesics which predispose population segments and individuals to narcotic addiction. These include social pathology and personality disorders. The narcotic analgesics are especially prone to abuse because they can produce both a high, elated feeling (positive pleasure) and relief from fear, pain, and anxiety (negative pleasure). In addition, tolerance develops rapidly to these effects and a state of physical dependence is produced which becomes manifest as an abstinence syndrome. Although the abstinence syndrome is not a life-threatening disease, it is

very unpleasant to the addict and provides a strong drive and motive for drug-seeking behavior and abuse. Many addicts relapse after treatment. The reason for this is not known; however, several factors are suspected: (a) those conditions that were responsible for initial experimentation with drugs, (b) there may be a protracted hyperirritable state that may persist for many months, (c) abstinence signs may be conditionable, and environmental circumstances associated with drug-seeking behavior may evoke conditioned abstinence which may lead to drug-seeking behavior and relapse. Thus drug addiction is like many diseases, in that there are many factors that define individual susceptibility.

319. Martin, W.R., Fraser, H.F., Gorodetzky, C.W., and Rosenberg, D.E.: Studies of the dependence-producing potential of the narcotic antagonist 2-cyclopropylmethyl-2'-hydroxy-5,9-dimethyl-6,7-benzomorphan (cyclazocine, Win-20,740; ARC II–C–3). *The Journal of Pharmacology and Experimental Therapeutics* 150:426–436 (1965).

The effects of single doses and chronic administration of cyclazocine have been studied in nontolerant postaddicts, as well as in postaddicts physically dependent upon morphine. In addition, cyclazocine has been compared with morphine sulfate and nalorphine hydrochloride. Single dose studies indicate that cyclazocine produces a degree of euphoria, and that maximal euphoric effects are produced with doses of the order of magnitude of 1 mg/70 kg. The subjective effects produced by cyclazocine, however, are qualitatively different from those produced by morphine and most closely resemble those of nalorphine. In addition, larger doses of cyclazocine (1.0 and 2.0 mg/kg) produced certain effects which resembled, at least superficially, those produced by barbiturates. Cyclazocine does not suppress abstinence in subjects physically dependent on morphine; on the contrary, it precipitates abstinence in a manner similar to that of nalorphine. Subjects chronically intoxicated with 13.2 mg/70 kg/day of cyclazocine, using a gradually progressing dose schedule, showed definite evidence of tolerance to cyclazocine, cross-tolerance to nalorphine, and exhibited a definite abstinence syndrome when cyclazocine was withdrawn. The predominant signs of abstinence from cyclazocine consisted of an increase in body temperature, mydriasis, loss of appetite, decrease in body weight, and tachycardia. The abstinence syndrome was slow in developing, first becoming apparent on the third or fourth day following withdrawal, and reaching a maximum on the seventh day of abstinence. Minimal signs of abstinence were seen as long as 6 weeks following withdrawal. The abstinence syndrome was qualitatively different from that from morphine. Although cyclazocine produces a type of euphoria, tolerance, and physical dependence, the bulk of evidence indicates that

this agent is qualitatively different from morphine. In general, the effects of cyclazocine most closely resembled those of nalorphine. In conclusion, cyclazocine should not be classified as a morphinelike analgesic and its potential for abuse by narcotic addicts is regarded as being very low. Whether it would be abused on the basis of other pharmacologic properties, particularly for its sedative characteristics, cannot be predicted on the basis of these experiments.

320. MARTIN, W.R. and GORODETZKY, C.W.: Demonstration of tolerance to and physical dependence on N-allylnormorphine (nalorphine). *The Journal of Pharmacology and Experimental Therapeutics* 150:437–442 (1965).

Nalorphine was administered chronically to seven subjects, using progressively increasing dose levels, to determine if tolerance and physical dependence would develop. Both physiologic and subjective responses were studied. During the course of chronic intoxication with nalorphine, it became apparent that subjects became tolerant to the effects of nalorphine and were cross-tolerant to the subjective effects of the narcotic antagonist cyclazocine. When abruptly withdrawn from nalorphine all subjects exhibited an abstinence syndrome which was qualitatively different from the morphine abstinence syndrome but closely resembled the abstinence syndrome seen in patients who had received large doses of cyclazocine. The studies provide additional support for the hypothesis (Martin et al., 1965) that the narcotic antagonists produce a type of physical dependence that is qualitatively different from that produced by the narcotic analgesics. The abstinence syndrome seen following withdrawal from large doses of narcotic antagonists causes only mild discomfort and does not seem to give rise to compulsive drug-seeking behavior.

321. MULÉ, S.J.: Distribution of N-C^{14}-methyl labeled morphine III. Effect of nalorphine in the central nervous system and other tissues of tolerant dogs. *The Journal of Pharmacology and Experimental Therapeutics* 148:393–398 (1965).

The administration of 2 mg/kg of N-C^{14}-methyl labeled morphine to tolerant dogs, followed in 35 minutes by 2 mg/kg of nonlabeled nalorphine, resulted in a statistically significant decrease (42 to 56 percent) in central nervous system levels of morphine at 65 minutes, and no real change at either 165 or 275 minutes following the labeled drug. Nalorphine caused a reduction of 5 to 73 percent in the levels of morphine at each time interval in the heart, lung, liver, and kidney. Chromatographic studies of the central nervous system extracts of nalorphine antagonized dogs provided no evidence for the existence of an N-C^{14}-methyl labeled metabolite of morphine. The plasma levels of free mor-

phine in the nalorphine antagonized dog were essentially lower than control values between 30 and 275 minutes following drug administration. Conjugated morphine levels in the plasma were lower in control animals as compared to the antagonized dogs between 60 and 180 minutes after labeled morphine, and similar between 180 and 275 minutes. The CSF levels of morphine in the antagonized dogs were lower than control levels at 65 and 275 minutes following drug administration.

322. O'Donnell, J.A.: Narcotic addiction. In: Lurie, H.L. (ed.): *Encyclopedia of Social Work* (ed. 15), pp. 522–526. New York: National Association of Social Workers, 1965.

323. Wikler, A.: Conditioning factors in opiate addiction and relapse. In: Wilner, D.M. and Kassebaum, G.G. (eds.): *Narcotics*, pp. 85–100. New York: McGraw-Hill, 1965.

This paper presents the two-factor learning theory of relapse to narcotics, in which the role of conditioning in physical dependence and abstinence as well as operant drug-seeking behavior are put forth, as well as experimental data supporting this hypothesis.

324. Wikler, A., Haertzen, C.A., Chessick, R.D. Hill, H.E., and Pescor, F.T.: Reaction time ("mental set") in control and chronic schizophrenic subjects and in postaddicts under placebo, LSD–25, morphine, pentobarbital and amphetamine. *Psychopharmacologia* 7:423–443 (1965).

Auditory-manual reaction times, 2, 3.5, 5, 10, and 20 s after flashing of a "warning" light, both on "irregular" and "regular" schedules of preparatory intervals, were measured under "no medication" conditions in 10 personnel control and 13 chronic schizophrenic subjects, as well as in "postaddicts" after administration of placebo, LSD–25, morphine, pentobarbital, or amphetamine. Each subject was tested twice under each condition (no medication, placebo, or drug) on different days, once with the "irregular" procedure preceding the "regular" and again in the reverse order. Comparisons of the effects of treatment (placebo or drugs) on mean reaction times of "postaddicts" with mean reaction times of personnel controls and schizophrenic subjects were based on the "combined order" data (average of the two "irregular" and the two "regular" data under each condition). Compared with personnel controls, mean reaction times of chronic schizophrenic subjects were significantly longer, variance due to difference in procedure ("irregular" or "regular") was significantly smaller, and shortest reaction times

tended to occur at the 3.5-s interval (rather than at the 2-s interval). In the "postaddict" group under the placebo condition, mean reaction times on the "irregular" procedure were shorter than in the personnel control group, with consequent reduction of variance due to difference in procedure. At a dose level of 1.0 μg/kg, LSD–25 prolonged reaction times on the "irregular" procedure, thereby "normalizing" the relationships between the "irregular" and "regular" curves. LSD–25 at the dose level of 2.0–3.0 μg/kg, morphine (15 and 30 mg), and pentobarbital (250 mg) all prolonged reaction times significantly and produced a trend for occurrence of shortest reaction times at the 3.5-s interval on the "regular" procedure. While these treatments did not affect reaction times on the "irregular" and "regular" procedures differentially, indirect evidence suggests that they did impair the ability of "postaddicts" to profit from regularization of the presentation of preparatory intervals. Amphetamine had no effect except to shorten reaction times to some extent. It is concluded that LSD–25 (2.0–3.0 μg/kg), morphine, and pentobarbital produce changes in "mental set" qualitatively similar to that which characterizes patients with schizophrenia, but that the nature of such impairment is not specific for schizophrenia, except possibly in degree.

325. Wikler, A., Rosenberg, D.E., Hawthorne, J.D., and Cassidy, T.M.: Age and effect of LSD–25 on pupil size and knee jerk threshold studies in chronic schizophrenic and nonpsychotic subjects. *Psychopharmacologia* 7:44–56 (1965).

The effects of placebo and of LSD–25 at two-dose levels (0.5 and 1.5 μg/kg), all injected intramuscularly, on pupil diameter (photographic method) and knee-jerk threshold (pendulum hammer) were measured in five chronic schizophrenic and five nonpsychotic control subjects matched as closely as possible for age and weight. No significant differences were found between the two groups as regards extent of pupil dilation or of decrease in knee-jerk threshold produced by either dose of LSD–25, or with respect to the differences in magnitudes of effect of the two doses. For the two groups combined (N=10), significant negative correlations were found between age and initial (preinjection) pupil diameter, and between age and pupillary response to LSD–25, while the latter was found to correlate positively with initial pupil diameter. In contrast, no significant correlations were found between age and initial knee-jerk threshold, age and decrease in threshold produced by either dose of LSD–25, or between the latter and initial knee-jerk threshold. It is concluded that some as yet unknown factors involved in the aging process influence not only initial pupil size but also pupillary responsivity to LSD–25, and that control of the age variable is particularly important in any study on autonomic functioning.

1966

326. Ball, J.C., Bates, W.M., and O'Donnell, J.A.: Characteristics of hospitalized narcotic addicts. *HEW Indicator*, pp. 17–26, Mar. 1966.

The records of the two U.S. Public Health Service hospitals for addicts, from their openings in 1935 and 1938 through 1964, are used to show changes in the demographic characteristics of patients. There was a marked drop in mean age at first admission; among males, about 16 percent were under age 30 in 1935, as against 50 percent in 1963. Percent nonwhite increased over the same interval, from under 20 percent to over 40 percent. Early admissions came from many States, with over a third from the South; by 1963 admissions from the South had dropped markedly, with large increases in admissions from New York and Illinois. Admissions were increasingly from metropolitan areas.

327. Ball, J.C., Cottrell, E.S., and O'Donnell, J.A.: Selected social characteristics of consecutive admissions to Lexington in 1965. *Criminologica* 4:13–16 (1966).

The admissions to the Lexington hospital in 1965 are examined to throw light on the association between addiction and criminality. Of 1693 admissions, 84 percent gave histories of one or more arrests. The age at first arrest tended to precede age at first use of opiates; the median ages were 18.4 and 20.0, respectively, for males and 20.8 and 22.6 for females. When questioned about means of support during the 6 months prior to admission, only 35 percent of males claimed legal employment; one-third admitted illegal occupations.

328. Essig, C.F.: Barbiturate withdrawal in white rats. *International Journal of Neuropharmacology* 5:103–107 (1966).

Crossland and Leonard (1963) first reported that the white rat will develop physical dependence on sodium barbital if fluid intake is restricted to solutions containing increasing concentrations of that drug. Convulsions occurred in such rats following the withdrawal of sodium barbital. The study reported here was based on the same method. Two groups of male Wistar rats were addicted to mean final dose levels of 396 mg/kg in 111 days (group I) and 313 mg/kg in 159 days (group II). Both groups of rats were hypothermic at the end of addiction, and group I rats lost a significant amount of weight during the same period. Following barbital withdrawal both generalized tonic-clonic and partial convulsions were observed. Other manifestations of abstinence were reduction in food and water consumption as well as weight loss. Perhaps the continuous availability of barbital and its more frequent intake favor

the development of physical dependence. Previous unsuccessful attempts to induce in rats physical dependence on the barbiturates were based on the single daily dose method of administering the drug.

329. Essig, C.F.: Newer sedative drugs that can cause states of intoxication and dependence of barbiturate type. *Journal of the American Medical Association* 196:714–717 (1966).

Seven of the newer nonbarbiturate sedative-hypnotic drugs have been reported to cause barbituratelike states of intoxication or physical dependence, or both, if abused. These drugs are meprobamate, glutethimide, ethchlorvynol, ethinamate, methyprylon, chlordiazepoxide, and diazepam. Excessive use of one or more of these drugs can cause drowsiness, difficulty in thinking, and incoordination of movement. These signs of intoxication are similar to those induced by barbiturates or alcohol and are conducive to vehicular accidents, injury by falling, interference with occupational skills, and violent or assaultive behavior. If physical dependence has been established to one or more of these drugs, abrupt withdrawal thereof can result in a serious abstinence syndrome. The minor manifestations of withdrawal are anxiety, tremulousness, muscle twitches, anorexia, weakness, and insomnia. Major signs of sedative-hypnotic drug withdrawal are generalized convulsions or a delirium, with psychotic manifestations such as disorientation, delusions and hallucinations, or both. Death has been attributed to withdrawal of meprobamate and methyprylon. Treatment must be carried out in the hospital and requires barbiturate substitution, followed by its gradual withdrawal at a rate not to exceed 0.1 gm daily. Diphenylhydantoin and phenothiazine derivatives are not effective against the abstinence convulsions.

330. Essig, C.F. and Flanary, H.G.: The importance of the convulsion in occurrence and rate of development of electroconvulsive threshold elevations. *Experimental Neurology* 14:448–452 (1966).

Daily electrical stimulation of the brain in progressive increments until a major convulsion develops results in an increasing elevation of the threshold for such convulsions in cats. There has been no study made of the role, if any, of the subconvulsive electrical stimuli in the electroconvulsive threshold (ECT) elevation phenomenon. This report describes the first experiments, known to the authors, made to determine whether the ECT elevation phenomenon is due entirely or in part to the subconvulsive electrical stimuli which precede the electroconvulsion itself. It was found that repeated subconvulsive electrical stimuli, that did not culminate in a major convulsion, failed to elevate the ECT threshold. In contrast, repeated supramaximally induced electroconvulsions without prior subconvulsive electrical stimulation caused a sig-

nificant elevation of the ECT. It was also determined that inducing four electroconvulsions daily for 20 days caused a significantly greater increase in the ECT than either one or two such seizures daily during an equal period of time. It was concluded that the tolerancelike response to electrically induced convulsions depends on mechanisms related to the convulsive process itself more than the stimulus of origin.

331. Essig, C.F. and Fraser, H.F.: Failure of chlorpromazine to prevent barbiturate withdrawal convulsions. *Clinical Pharmacology and Therapeutics* 7:466–469 (1966).

In dogs, as well as in men, addicted to barbiturate, withdrawal may be associated with convulsions, delirium, and even death. Withdrawal at a rate not exceeding 0.1 gm daily is a safe and effective method of overcoming the barbiturate abstinence syndrome. Chlorpromazine has been advocated for the treatment of this serious withdrawal phenomenon. Dogs were used in this study to test the effects of chlorpromazine at various dose levels on barbital-withdrawal convulsions. Chlorpromazine in dosages ranging from 1 mg/kg every 4 hours to 32 mg/kg every 12 hours failed to suppress the convulsions. Chlorpromazine also failed to suppress the restlessness, tremulousness, twitching, and increased startle response that occur during the week following withdrawal of barbiturate in the dogs. On the basis of these observations in the dog, it is recommended that chlorpromazine not be used in the treatment of barbiturate-withdrawal manifestations in man.

332. Haertzen, C.A.: Changes in correlation between responses to items of the Addiction Research Center Inventory produced by LSD–25. *Journal of Psycho-Pharmacology* 1:27–36 (1966).

The following conclusions are drawn: LSD alters intercorrelations between responses on items that reflect its effects and thereby alters factor structure. Hence, some support for Cattell's theory (1952) is presented. This finding gives a theoretical justification for using responses under specialized environments as predictors of criterion responses. A general rationale for prediction is the degree of similarity of conditions. Changes in intercorrelations of responses from no-drug or placebo to LSD are much less than the changes in probability of responses between no-drug and LSD. Consistency of response between no-drug and LSD generally accounts for more variance of response than does the difference between these experimental conditions. To the author's knowledge, no prior criterion analyses of drug effects have been attempted. The results of the present study support the validity and efficacy of drug scales since the differences between no-drug and drug conditions are correlated with first factor loadings, and provide a logical and sufficient (though not a necessary) basis for an expectation of

reliable scales. The generality of this finding was subsequently tested with six other drugs (Haertzen, 1962) in a criterion analysis that bears some similarity to Eysenck's classical criterion analyses (1950). In each case, estimates of first factor loadings for different drug scales were correlated with corresponding drug-placebo differences. A subsequent report will deal with this criterion analysis in greater detail.

333. Haertzen, C.A.: Development of scales based on patterns of drug effects, using the Addiction Research Center Inventory (ARCI). *Psychological Reports* 18:163–194 (1966).

A series of scales were developed on the basis of the pattern of change of responses on Addiction Research Center Inventory items produced by drugs including morphine, pentobarbital, chlorpromazine, alcohol, LSD, pyrahexyl, and amphetamine in postaddicts. The pattern scales were compared with empirically developed scales that measure the effects of each drug as contrasted with placebo. It was found that the empirical scales show a greater sensitivity to general or nonspecific drug effects than pattern scales, i.e., all drugs in the series produced significant elevations on empirical scales. Because of this characteristic, less differentiation between drugs is possible with empirical scales. On scales which reflect patterns of drug actions, greater differentiation between drugs was shown. Higher doses produced more specific drug effects than lower doses. This difference was produced probably by a relatively greater contribution of nonspecific drug effects for lower doses. Significant reliability coefficients were obtained for all scales. Reliability of scales across conditions was related to the type of scale and similarity of conditions. As indicated by several findings, condition-similarity has implications for relating personality to drug effects.

334. Haertzen, C.A. and Horine, I.: Noncomparability of the 1950 and 1956 forms A of Cattell's sixteen personality factor questionnaire. *Psychological Reports* 18:342 (1966).

Cattell and his associates developed three forms of the 16 PF which have been revised periodically. Cattell appears to regard the editions as equivalent. This evaluation is attested by the repetition of the same means of various samples in the two handbooks cited above. Interest in the similarity of revisions grew out of an attempt to compare alcoholics who had been given the 1956 form A and opiate addicts who had been tested with the 1950 form A. Since the differences on several scales were larger than expected, an attempt was made to determine whether differences could be ascribed to the forms rather than the groups. To test for equivalence of the 1950 form A and the 1956 form A, the two forms were given in randomized order 1 wk apart to 33 postopiate addicts.

Scores were converted to stens, using adult norms in the undated tabular supplements of the "Handbook for the Sixteen Personality Factor Questionnaire." F ratios for the differences between means for repeated observations and cross-scale product-moment correlations for the 16 scales were determined. Significant differences ($p \leq .05$) obtained on 11 scales. Mean sten scores on the 1950 Form A were significantly higher than those on the 1956 form A on scales C, E, and H and significantly lower on scales I, L, M, N, O, Q_1, Q_2, and Q_4. Cross-form reliability coefficients were not significant on scales A, G, M, N, and Q_1. Only one reliability coefficient on scale 1 was above .70. Other investigators using the 1950 and 1956 revisions have concluded that the N scales of forms A and B do not measure the same thing. It is concluded that a number of 16 PF scales in the 1950 and 1956 form A tests do not measure the same individual difference factors in this sample of opiate addicts. Caution, therefore, needs to be exercised in generalizing results across revisions of the test. More research needs to be devoted to methodology for providing equivalent personality scales. It would, of course, be beneficial to users of the 16 PF if the authors would comment on the editions and indicate the form and edition of the test associated with tables and results when a new manual is published.

335. Hill, H.E., Belleville, R.E., Pescor, F.T., and Wikler, A.: Comparative effects of methadone, meperidine and morphine on conditioned suppression. *Archives Internationales de Pharmacodynamie et de Therapie* 163:341–352 (1966).

Methadone and meperidine were compared with morphine as to effectiveness in reducing a conditioned emotional response (CER) in rats, using conditioned suppression as an index of emotion. The decrement in lever pressing for food reinforcement induced by repeated tone-shock conditioning was decreased in proportion to the dose of the three drugs. Quantitative differences were found, but qualitatively these analgesics appeared to be equally effective. An unexpected and provocative finding was that the ED_{50} for each of these drugs on the very complex behavior involved in conditioned suppression was very similar to that found by other investigators, using unconditioned "skin-twitch" and "tail-flick" reactions. The possible significance of reduction of CER under particular experimental conditions is discussed in relation to the induction of analgesia.

336. Isbell, H. and Gorodetzky, C.W.: Effects of the alkaloids of ololiuqui in man. *Psychopharmacologia* 8:331–339 (1966).

Five mg of either a crude extract of seeds of ololiuqui or a mixture of synthetic alkaloids caused drowsiness in former morphine addicts but few other subjective effects. Perceptual distortion was reported only

rarely, and hallucinations did not occur. In contrast, LSD–25 caused nervousness, perceptual distortion, euphoria, and hallucinations. The alkaloids of ololiuqui did not cause fever or marked mydriasis. Ololiuqui and alkaloids of ololiuqui should be regarded principally as sedatives rather than as psychotomimetics.

337. Jones, B.E. and Ayres, J.J.B.: Significance and reliability of shock induced changes in basal skin conductance. *Psychophysiology* 2:322–326 (1966).

Once weekly for 5 weeks, 15 adult male postaddicts were given 12 to 15 shocks of 5.0 to 8.0 mA. Basal skin conductance (BSC) was recorded during the 25-min weekly sessions. Increases in BSC during each session and the week-to-week reliabilities of the increases were determined. After the first week, subsequent increases showed reliability coefficients which ranged from 0.69 to 0.95 ($P<0.01$). The reliabilities of the increases in BSC produced by shock were considered favorable for the use of change in BSC as a dependent variable in designs requiring repeated measurements on the same Ss at weekly intervals.

338. Martin, W.R.: Assessment of the dependence producing potentiality of narcotic analgesics. In: Radouco-Thomas, C. and Lasagna, L. (eds.): *International Encyclopedia of Pharmacology and Therapeutics*, Sect. 6, Vol. I, pp. 155–180. Glasgow: Pergamon Press, 1966.

Methods used in assessing the abuse potentiality of narcotic analgesics are described. Further, a summary of the literature showing how the effects of graded doses of a variety of morphinelike analgesics and subjective effect questionnaires covary with pupillary diameter measured in the same subjects and the analgesic effects of these drugs measured in other subjects covary. An analysis of data obtained using the substitution and direct addiction tests for measuring the ability of a variety of narcotic analgesics to produce physical dependence are also described and the concordance between these results and those obtained using single dose studies are discussed and compared. Finally, the results of these techniques used to assess the abuse potentiality of narcotic analgesics are further validated using "street" incidence of abuse.

339. Martin, W.R.: Pharmacologic factors in relapse and the possible use of the narcotic antagonists in treatment. *Illinois Medical Journal* 130:489–494 (1966).

The roles of conditioned abstinence and drug-seeking behavior as well as protracted abstinence in relapse are discussed. Further, the possible utility of narcotic antagonists such as cyclazocine in psychological extinction of conditioned drug-seeking behavior and abstinence as well as physiologic extinction of protracted abstinence is developed.

340. Martin, W.R., Gorodetzky, C.W., Kay, D.C., McClane, T.K., and Jasinski, D.R.: Activities of the Addiction Research Center during 1965. *Committee on Problems of Drug Dependence*. Washington, D.C.: National Academy of Sciences, National Research Council, 1966.

341. Martin, W.R., Gorodetzky, C.W. and McClane, T.K.: An experimental study in the treatment of narcotic addicts with cyclazocine. *Clinical Pharmacology and Therapeutics* 7:455–465 (1966).

The potent narcotic antagonist, cyclazocine, has a long duration of action and is effective when administered orally. Although tolerance develops to many of the effects of cyclazocine, including dysphoria and sedation, tolerance does not develop to the drug's ability to antagonize the toxic, euphoric properties of morphine. Subjects who had received cyclazocine orally twice daily on a continuing basis experienced only a mild degree of euphoria when given very large doses of morphine, and developed only a very mild degree of physical dependence after continued administration of large doses of morphine. Cyclazocine antagonizes pharmacological actions of importance in the addiction to narcotic analgesics, and it could be useful in the ambulatory treatment of the abstinent addict.

342. Mulé, S.J.: Effect of morphine and nalorphine on the metabolism of phospholipids in guinea pig cerebral cortex slices. *The Journal of Pharmacology and Experimental Therapeutics* 154:370–383 (1966).

Studies were initiated to determine whether morphine and nalorphine would alter phospholipid metabolism in brain tissue. Slices of guinea pig cerebral cortex were incubated in 2 ml of Krebs-Hensleit bicarbonate saline containing 11.1 μmol of glucose for 2 hr at 37° C. Each vessel contained either P_i^{32}, glycerol-1,3-C^{14}, or *myo*-inositol-C^{14}. Morphine and nalorphine were added alone or together in final concentrations of 10^{-2} to 10^{-6}M. The phospholipids were extracted in chloroform-ethanol (1:1, v/v) and chromatographed on silicic acid-impregnated paper using the solvent diisobutyl ketone-acetic acid-water (40:25:5, v/v). Polyphosphoinositides were separated using the solvent phenol-concentrated NH_3 (99:1, v/v). Autoradiograms were prepared and the labeled phospholipid spots were carefully cut out and counted. Morphine and nalorphine (10^{-2}–10^{-3} M) significantly stimulated the incorporation of P_i^{32} into lysophosphatidylinositol, phosphatidylinositol, phosphatidylserine, phosphatidylethanolamine, phosphatidic acid, and diphosphoinositide about 26 to 299 percent and inhibited the uptake of P_i^{32} into phosphatidylcholine 46 to 59 percent. A significant stimulation (24–83 percent) was still evident for certain phosphatides in the presence of 10^{-6} M nalorphine. Nalorphine (10^{-2}–

10^{-6} M) did not appear to consistently alter the effect of 10^{-2} M morphine on phospholipid metabolism. The data obtained with the C^{14}-labeled precursors were quite similar to data observed with P_i^{32}. The results suggest that D-1,2-diglyceride, an essential intermediate in the biosynthesis of glycerophosphatides, becomes limiting.

343. Mulé, S.J. and Gorodetzky, C.W.: Physiological disposition of H^3-cyclazocine in nontolerant, tolerant and abstinent dogs. *Committee on Problems of Drug Dependence.* Washington, D.C.: National Academy of Sciences, National Research Council, 1966.

344. Mulé S.J. and Gorodetzky, C.W.: Physiologic disposition of H^3-cyclazocine in nontolerant and abstinent dogs. *The Journal of Pharmacology and Experimental Therapeutics* 154:632–645 (1966).

This study was initiated in order to correlate the distribution and metabolism of H^3-cyclazocine with its pharmacologic effects. A method specific for the estimation of H^3-cyclazocine in biologic tissue and fluids was developed with a minimal sensitivity of 3 ng/ml of biologic material. Urine, fecal, and plasma levels were determined in the same nontolerant, tolerant, and abstinent dogs following a 1.25-mg/kg (free base) subcutaneous injection of H^3-cyclazocine. The mean percentage recovery of the administered dose from urine and feces for both free and conjugated drug over a period of 120 h was 43.7 percent from nontolerant dogs, 58.5 percent from tolerant dogs and 40.7 percent from abstinent dogs. Mean plasma levels of free cyclazocine reached a maximum of 156 ng/ml at 30 min in both nontolerant and tolerant dogs, and then fell rapidly to a level of 6 ng/ml at 8 h in these dogs. Maximal levels of 304 and 361 ng/ml of conjugated cyclazocine were found at 90 min in the nontolerant and tolerant dogs, respectively. Mean values of 60 to 80 ng/ml of conjugated cyclazocine were obtained for these animals at 8 h. Maximal mean levels of 1,215 and 1,259 ng/g were obtained at 1 h in cerebral cortex gray matter of nontolerant and tolerant dogs, respectively. In white matter, the mean levels were 895 to 1,108 ng/g. At 6 h, the values had fallen to 36 to 56 ng/g in nontolerant dogs, and 100 to 117 ng/g in tolerant dogs. The levels of drug in subcortical areas were similar to those observed in the cerebrum. No drug was found in the central nervous system of a 24-h abstinent dog. The levels of drug in certain peripheral tissues paralleled central nervous system values, but were quite high in lung, kidney, spleen, liver, and adrenals. The bile contained extremely high levels of free and conjugated drug. The results indicated that potency of cyclazocine but not latency of abstinence was correlated with distribution, and that the drug was markedly metabolized.

345. O'Donnell, J.A. and Ball, J.C.: *Narcotic Addiction.* New York: Harper & Row, 1966.

This book is a compilation of articles presenting the viewpoints of various disciplines (medicine, criminology, religion, etc.) on the causes, effects, and treatment of drug addiction.

346. O'Donnell, J.A.: Narcotic addiction and crime. *Social Problems* 13:374–385 (1966).

Data from a followup study of Kentucky addicts are related to other studies, and the combined findings interpreted as supporting two major conclusions. First, addicts have been more and more recruited from among persons with prior criminal records in recent decades, and today it is probable that most new addicts were criminals before their addiction. Second, they commit more crimes after their addiction than they would have been expected to commit. It is equally true, however, for this sample that many subjects did not have a criminal record either before or after addiction, and probable that a sizeable minority never committed criminal acts. A third finding of this study does not support the conclusions of others; here there was no evidence of a decrease in crimes of violence after addiction. Evidence is presented that the increase in crime after addiction is not a direct effect of the drug use, but is due to the way of life which becomes necessary in many cases, but not in all, to obtain narcotics.

1967

347. Ball, J.C.: Marijuana smoking and the onset of heroin use. *British Journal of Criminology* 7:408–413 (1967).

The question of how opiate use started among the Puerto Rican addicts of this study has been answered. Heroin use started in an unsupervised street setting, while the subjects were still teenagers. The youthful initiate usually had smoked marihuana with neighborhood friends before using opiates. In the case of both marihuana smoking and heroin use the adolescent peer group exercised a dominant influence. The incipient drug user asked his older addict friends to be included in the group's primary activity. As has been previously reported in the continental United States (Chein, 1964; Fort, 1954; Mayor's Committee on Marijuana, 1944), there was no evidence that the onset of drug use among the Puerto Rican addicts was a consequence of proselytizing, coercion, or seduction. Onset was, nonetheless, a group process. The incipient addict willingly sought to join the addict group and learn the techniques and norms of the drug subculture. He was not in this process

misled by "mercenary fraud." Finally, it is pertinent to note that the interpersonal and situational factors associated with the onset of marihuana smoking and opiate use among the Puerto Rican addicts of this study have not changed during the past 40 years. Although the incidence and prevalence of drug abuse in Puerto Rico may well have changed during this period, the evidence suggests that the peer-group behaviour leading to the onset of drug addiction has remained unchanged.

348. Ball, J.C.: The reliability and validity of interview data obtained from 59 narcotic drug addicts. *American Journal of Sociology* 72:650–654 (1967).

Using 59 patients from a followup study—all those on whom three sources of information were available, five items from interviews were compared with: (a) hospital records, (b) FBI arrest records, and (c) urine samples. Reliability was tested against hospital records for age, and age at onset of drug use; agreement on the first was close for males, less so for females, and less for both sexes on the second item. "Errors" tended to be split between early and late dates, so means would be little affected. Validity comparisons on first arrest and total arrests with FBI records showed a large majority gave correct information in the interview; discrepancies seemed explainable as the forgetting of minor offenses or differences in defining arrests, with no hint of deliberate underreporting. Of 25 urine specimens obtained from subjects "on the street," 18 negative and 5 positive laboratory findings corresponded to oral reports of drug use; 2 denied use, but laboratory reports were positive. Given careful research procedures, the reliability and validity of field interviews with addicts seemed quite high.

349. Essig, C.F.: Clinical and experimental aspects of barbiturate withdrawal convulsions. *Epilepsia* 8:21–30 (1967).

Clinical and experimental data concerning mechanisms underlying barbiturate withdrawal convulsions have been reviewed. Such abstinence seizures have occurred in decorticate and decerebellate dogs. The possible role of the reticular activating system in the origin of this convulsive process was discussed. An increase in neuronal excitability probably develops during barbiturate withdrawal, but a biochemical basis for this has not been proven.

350. Haertzen, C.A. and Fuller, G.B.: Subjective effects of acute withdrawal of alcohol as measured by the Addiction Research Center Inventory (ARCI). *Quarterly Journal of Studies on Alcohol* 28:454–467 (1967).

Four groups of male alcoholics (N = 163), who were withdrawn

from alcohol at the Willmar State Hospital, were given the Addiction Research Center Inventory (ARCI) with supplemental questions, on day 2, week 1, week 2 and week 3 after admission, to test for the acute effects of withdrawal of alcohol. Some subjects tested on day 2 were retested on weeks 1, 2, or 3, resulting in 50 tests for each period. Most subjects tested on day 2 had received chlorpromazine and chloral hydrate, and the examiner had to read the questions and mark the responses for some of them. Comparisons were made between the 4 groups on 26 ARCI scales. Subjects tested on day 2 were reliably and highly differentiated (by analysis of variance) from those tested on weeks 1, 2, and 3, but the differences among the weeks were negligible except in a subsample of subjects who experienced visual hallucinations during or after their last alcoholic spree. Alcohol withdrawal was similar in some respects to the acute effects of psychologically active drugs such as alcohol, pentobarbital, pyrahexyl, chlorpromazine, lysergide, morphine, and amphetamine as determined in opiate addicts. Part of the similarity is attributed to greater reactivity arising from changing internal stimuli. Alcohol withdrawal and the acute effects of the first five drugs are associated with a decrease of efficiency (tiredness, sluggishness, poor motivation, poor cognition); withdrawal is most opposite the effects of amphetamine in these respects. Anxiety and tension are common complaints under lysergide and withdrawal. Hostility, confusion, impatience, inadequacy, impulsivity, and neurotic sensitivity also increase somewhat during withdrawal.

351. Haertzen, C.A. and Navarro, S.O.: A single diagram for computation of tetrachoric correlations. *Journal of General Psychology* 77:263–265 (1967).

A method for the rapid calculation of tetrachoric correlations is presented which is simpler than older methods and employs a single computing diagram. One diagram is necessary for computation because marginal totals are equalized by dividing each marginal total by itself and multiplying by 100.

352. Haertzen, C.A. and Panton, J.H.: Development of a "psychopathic" scale for the Addiction Research Center Inventory (ARCI). *International Journal of the Addictions* 2:115–127 (1967).

An empirical psychopathic deviate scale (Pyp) for the Addiction Research Center Inventory (ARCI) was developed with 785 subjects by selecting items which differentiated presumed psychopathic (criminals, opiate addicts, and alcoholics) and nonpsychopathic groups (mentally ill and normal). The scale, consisting of 74 items, highly distinguished the psychopathic and nonpsychopathic groups and was significantly correlated with three independent measures of social deviation. Criminals

and addicts were most socially deviant, alcoholics were intermediate, and normal subjects were the least deviant. Better overall differentiation of pertinent groups is obtained with the Pyp scale than with other commonly used standard tests such as the MMPI, CPI, 16 P.F., and GZTS. It is thought that the psychopathic factor is a minor personality factor which accounts for only a small proportion of variability of responses to inventory questions which have negative social implications.

353. Hill, H.E., Bell, E.C. and Wikler, A.: Reduction of conditioned suppression: actions of morphine compared with those of amphetamine, pentobarbital, nalorphine, cocaine, LSD–25 and chlorpromazine. *Archives Internationales de Pharmacodynamie et de Therapie* 165:212–226 (1967).

Investigations on several drugs in reducing conditioned suppression of lever pressing of rats produced by conditioned emotional responses (CER) of two different strengths showed that morphine and LSD–25 produced significant dose-effect relationships when using the weaker CER, but that such effectiveness was not shown for amphetamine, pentobarbital, nalorphine, chlorpromazine, or cocaine. When using a more strongly conditioned emotional response only morphine produced significant dose-effect reduction of conditioned suppression. Thus, the data obtained in this series of studies indicate that the conditioned suppression technique may be useful in detecting potent analgesics and studying some of their mechanisms of action since methadone and meperidine produced effects similar to those of morphine. However, published data have been both confirmatory and contradictory. These results were discussed, as were various other types of studies which might provide clues as to the mechanisms of actions of drugs that reduce conditioned suppression of lever pressing.

354. Isbell, H., Gorodetzky, C.W., Jasinski, D., Claussen, U., Von Spulak, F., and Korte, F.: Effects of (−)-Δ^9-*trans*-tetrahydrocannabinol in man. *Psychopharmacologia* 11:184–188 (1967).

Δ^9-THC is about 2.6–3.0 times as potent when smoked as when taken orally. The effects of Δ^9-THC seem to be identical to those of crude marihuana or hashish. Objective effects include a dose dependent tachycardia and conjunctival injection. Subjective effects include euphoria, alterations in time sense, and sensory perceptual distortions. With doses of 300–480 μg/kg orally or 200–250 μg/kg by smoking, marked sensory distortion, derealization, depersonalization, and hallucinations occurred in most patients. Patients tolerant to LSD were not cross-tolerant to Δ^9-THC.

355. Isbell, H., Jasinski, D.R., and Gorodetzky, C.W.: Studies

on tetrahydrocannabinol. I. Method of assay in human subjects and results with crude extracts, purified tetrahydrocannabinols and synthetic compounds. *Committee on Problems of Drug Dependence.* Washington, D.C.: National Academy of Sciences, National Research Council, 1967.

l-Δ^1-3,4-*trans*-tetrahydrocannabinol (Δ^1-THC) causes subjective effects similar to or identical with those of marihuana or hashish. The effects of Δ^1-THC include alterations in mood, sensory perceptual distortion and, in high dose, depersonalization, illusions, delusions, and hallucinations. Δ^1-THC is a psychotomimetic drug. Marihuanalike effects of tetrahydrocannabinols can be assayed quantitatively in man using either or both the subjective responses or the increase in pulse rate. Δ^1-THC is 2.6 times as potent when smoked as when taken orally. Crude extracts of marihuana seemed to be more potent than would have been expected from their tetrahydrocannabinol content suggesting but not proving that materials other than tetrahydrocannabinol may contribute to the effect.

356. Jasinski, D.R., and Martin, W.R.: Assessment of the dependence-producing properties of dihydrocodeinone and codoxime. *Clinical Pharmacology and Therapeutics* 8:266–270 (1967).

Dihydrocodeinone and a new narcotic antitussive, codoxime, were compared in single doses with morphine in a crossover study to compare their ability to produce opiatelike euphoria. In addition, both drugs were substituted for morphine in seven chronically addicted subjects to determine their capacity to produce physical dependence. Results indicated both drugs definitely produced drug dependence of the morphine type.

357. Jasinski, D.R. and Martin, W.R.: Evaluation of a new photographic method for assessing pupil diameters. *Clinical Pharmacology and Therapeutics* 8:271–272 (1967).

A modified Polaroid closeup camera was used to obtain pupil photographs of seven bed-confined subjects dependent upon 240 mg of morphine daily. Nalorphine produced dose-related increases in pupillary diameter determined as postdrug changes from the mean of predrug controls. Analysis of the replicate predrug pupil diameter for these seven subjects over seven separate occasions indicated between subjects as the only significant variance source.

358. Jasinski, D.R., Martin, W.R., and Haertzen, C.A.: The human pharmacology and abuse potential of N-allylnoroxymorphone (naloxone). *The Journal of Pharmacology and Experimental Therapeutics* 157:420–426 (1967).

The narcotic antagonist naloxone was studied in man to determine if it produced behavioral effects and physical dependence and if it substituted for morphine in morphine-dependent subjects. When compared to placebo in 12 subjects in a crossover design, no or little activity was demonstrated for naloxone while, in contrast, the narcotic antagonists, nalorphine and levallorphan, constricted pupils, produced responses on the subject's and observer's single-dose opiate questionnaires and produced psychotomimetic and sedativelike responses in a "subjective drug effect" questionnaire. In 10 subjects, naloxone administered 1, 2, and 4 h before a test dose of morphine antagonized the effects of morphine. In morphine-dependent subjects, naloxone was seven times as potent as nalorphine in precipitating abstinence. In three subjects, no behavioral or physiologic changes were observed during chronic administration and withdrawal of naloxone; however, the ability of naloxone to antagonize the effects of a test dose of morphine persisted. It is concluded that naloxone does not have abuse potential of the morphine type since it does not produce subjective effects or physical dependence and precipitates abstinence in morphine-dependent subjects. Further, naloxone is distinguished from the narcotic antagonists, nalorphine, levallorphan, and cyclazocine, in that it does not constrict pupils or produce subjective effects, physical dependence or tolerance.

359. Kay, D.C., Gorodetzky, C.W., and Martin, W.R.: Comparative effects of codeine and morphine in man. *The Journal of Pharmacology and Experimental Therapeutics* 156:101–106 (1967).

This research sought to collate the effects of graded parenteral doses of codeine and morphine in 20 human male postaddicts. A six-point, double-blind, crossover bioassay was used to contrast these drugs. Single intramuscular doses of codeine phosphate (90, 180, and 360 mg/70 kg) and morphine sulfate (7.5, 15, and 30 mg/70 kg) were compared in their production of miosis, drug identifications, opiate signs, opiate symptoms, liking (observers), and liking (subjects). Using these parameters, valid potency estimates were obtained which indicate that morphine is 7 to 14 times more potent than codeine. No significant decrement of effect in the dose-response curve is demonstrated for either drug over these dose ranges for any of the parameters studied. Within these dose ranges, codeine and morphine produce notably similar patterns of identification, opiate signs, and opiate symptoms. Codeine and morphine have a similar time action course for all variables except miosis, where codeine shows a more rapid onset and shorter duration of effect. Relative potencies calculated on the basis of total or peak data do not seriously differ in this investigation.

360. Marquardt, W.G., Martin, W.R., and Jasinski, D.R.: The use of

the Polaroid C. U. Camera in pupillography. *International Journal of the Addictions* 2:301–304 (1967).

A modification of the Polaroid CU5 camera for use in pupillography is detailed, describing a baffle plate to eliminate the inherent "ring" of light which obscured the circumference of the pupil. A framing device aids in focusing and a millimeter scale provides a reference for measuring pupil diameter. Pupillary measurement is a valuable indicator of the action of narcotics in man.

361. MARTIN, W.R.: Clinical evaluation for narcotic dependence. In: Way, E. L. (ed.): *New concepts in pain and its clinical management,* pp. 121–132. Philadelphia: F.A. Davis Co. 1967.

The narcotic antagonists possess a number of agonistic effects, including production of analgesia, depression of certain nociceptive and polysynaptic reflexes, respiratory depression, miosis and production of sedative and dysphoric subjective effects, and perhaps production of physical dependence. It is not clear whether the various agonistic actions of these antagonists can be dissociated, although several lines of evidence suggest this possibility. Thus, the cyclazocine dose-response curve for pupillary constriction reaches a plateau at the 1-mg dose level. On the other hand, no plateau has been observed for the opiate sign and symptom dose-response relationship for dose levels up to 2 mg. Lasagna et al. (1964), who have studied cyclazocine in doses up to 2 mg, have reported that 0.25 mg produces maximal analgesia and respiratory depression. Although these are thin lines of evidence, they suggest that the sedative and dysphoric actions of the narcotic antagonists can be dissociated from their miotic, respiratory depressant, and perhaps analgesic actions.

362. MARTIN, W.R.: Opioid antagonists. *Pharmacological Reviews* 19:463–521 (1967).

This review argues that narcotic analgesics are agonists at a morphine receptor and that antagonists such as nalorphine and cyclazocine are competitive antagonists at the morphine receptor and agonists at a nalorphine receptor. The agonistic actions of the narcotic antagonists as well as their antagonistic activity are reviewed in detail, and a variety of types of data, including a theoretical kinetic formulation, are used to develop the two-receptor theory of the actions of opioid antagonists. Finally, the clinical application and uses of the narcotic antagonists are described, including their ability to antagonize opioid-induced respiratory depression and analgesia, their utility in determining the abuse potentiality of analgesic drugs, their usefulness in diagnosing physical dependence of the morphine type, and their role in the treatment of abstinent narcotic abusers.

363. Martin, W.R. and Eades, C.G.: Pharmacological studies of spinal cord adrenergic and cholinergic mechanisms and their relation to physical dependence on morphine. *Psychopharmacologia* 11:195–223 (1967).

The effects of adrenergic and cholinergic antagonists and agonists were assessed on the flexor reflex (evoked by electrical stimulation) of the chronic spinal dog. Further, the role of adrenergic and cholinergic antagonists was assessed on the flexor reflex of the morphine dependent and abstinent chronic spinal dog. It was found that phenoxybenzamine had no significant effect on the flexor reflex; whereas, acute reserpine treatment enhanced this reflex. Amphetamine, methoxamine, and N-isopropylmethoxamine increased the amplitude of the flexor reflex and caused either fragmentary or continuous running movements. Chronic reserpine treatment, which decreased the excitability of the flexor reflex, antagonized the effects of amphetamine but did not significantly alter the effects of methoxamine or N-isopropylmethoxamine. Phenoxybenzamine antagonized the effects of all three agonists. Neither atropine nor methylatropine affected the amplitude of the flexor reflex. Physostigmine in the presence of methylatropine enhanced the flexor reflex. Atropine antagonized the enhancement produced by physostigmine. Phenoxybenzamine did not depress the amplitude of the flexor reflex in the abstinent chronic spinal dog; whereas, atropine produced a significant depression. These experiments suggest that although there are neither adrenergic nor cholinergic synapses in the segmental pathway that mediate the flexor reflex, there are adrenergic and muscarinic cholinergic facilitatory neurones that modulate this reflex. These facilitatory pathways seem to be independent. Further, it has been concluded that adrenergic pathways do not play a role in the genesis of spinal cord signs of the morphine abstinence syndrome in the chronic spinal dog; whereas, cholinergic neurones do participate in this syndrome.

364. Martin, W.R. and Gorodetzky, C.W.: Cyclazocine, an adjunct in the treatment of narcotic addiction. *International Journal of the Addictions* 2:85–93 (1967).

The pharmacologic properties of cyclazocine that make it useful in the treatment of abstinent narcotic addicts are reviewed, as well as the theoretical basis for its utility.

365. Martin, W.R., Jasinski, D.R., and Sapira, J.D.: Progress report on the assessment of the ability of GPA–1657 to produce drug dependence of morphine type in man. *Committee on Problems of Drug Dependence.* Washington, D.C.: National Academy of Sciences, National Research Council, 1967.

It is concluded that GPA–1657 in man produces a pattern of effects, as measured with pupillography, single-dose opiate questionnaires and a "subjective drug effect" questionnaire, which resemble those of morphine and has not produced a pattern of effects which are similar to nalorphine.

366. Martin, W.R., Jasinski, D.R., Sapira, J.D., Flanary, H.G., Van Horn, G.D., Thompson, A.K., Kelly, O.A., and Logan, C.R.: Drug dependence of the morphine type: physiological parameters—tolerance, early abstinence, protracted abstinence. *Committee on Problems of Drug Dependence.* Washington, D.C.: National Academy of Sciences, National Research Council, 1967.

367. McClane, T.K. and Martin, W.R.: Antagonism of the spinal cord effects of morphine and cyclazocine by naloxone and thebaine. *International Journal of Neuropharmacology* 6:325–327 (1967).

Both naloxone, a potent narcotic antagonist, and thebaine, a convulsant morphine analogue, can stimulate the flexor reflex of the chronic spinal dog and can antagonize the depressant effects on this reflex of both morphine and cyclazocine, another antagonist. Since naloxone can antagonize at a dose which does not stimulate the reflex, and thebaine can only antagonize at a stimulatory dose, we suggest that naloxone may antagonize directly at the morphine and cyclazocine receptor sites, whereas thebaine may antagonize indirectly through its stimulant effect at different receptors.

368. McClane, T.K. and Martin, W.R.: Effects of morphine, nalorphine, cyclazocine, and naloxone on the flexor reflex. *International Journal of Neuropharmacology* 6:89–98 (1967).

Morphine and cyclazocine can almost completely depress the flexor reflex of the chronic spinal dog, while nalorphine causes only partial depression. The slope of the morphine dose-response line is significantly steeper than that of the cyclazocine line, and the slope of the nalorphine line is intermediate. Naloxone, another narcotic antagonist, does not depress the reflex and in large doses enhances it. Reflex depression by these drugs is inversely proportional to the strength of the nociceptive stimulus. These data indicate that the flexor reflex is a valid method for assessing the potency of narcotics and narcotic antagonists and compares favorably with clinical methods in its sensitivity. The data also indicate that these drugs can differ in apparent intrinsic activity and that the discrepancy between the analgesic activity of narcotic antagonists in man and in several animal tests may merely reflect differences in sensitivity among the various methods for assessing analgesia.

369. Mulé, S.J.: Morphine and the incorporation of P_i^{32} into brain phospholipids of nontolerant, tolerant and abstinent guinea pigs. *The Journal of Pharmacology and Experimental Therapeutics* 156:92–100 (1967).

This investigation was initiated to determine the effect of administered morphine on the incorporation of P_i^{32} into cerebral cortex phospholipids from nontolerant, tolerant, and abstinent guinea pigs. After a single 40-mg/kg (free base) s.c. injection of morphine, guinea pigs were sacrificed 1, 4, and 10 h later. Cerebral cortex slices from these guinea pigs were incubated without and with the addictions of 10^{-2} to 10^{-6} M morphine. A significant stimulation (42–115 percent) of the incorporation of P_i^{32} into the phospholipids was observed with cortical slices incubated without additional morphine from animals sacrificed at 1 h P_i^{32} uptake into phosphatidylinositol phosphatidylcholine, phosphatidylserine, and phosphatidylethanolamine was significantly stimulated (45 to 112 percent) in cortical slices incubated without additional morphine from animals sacrificed at 4 h. Essentially no effect on the phosphatides was obtained with in vivo levels of morphine from guinea pigs sacrificed 10 h after drug. Absence of an effect on phospholipid metabolism was observed with cortical slices incubated without additional morphine from chronically morphine-treated animals. The effect of additional morphine (10^{-2}–10^{-6} M) on the phosphatides of slices from these animals appeared to be less than that found with nontolerant animals. No phospholipid effect occurred with cortical slices from abstinent guinea pigs (24 h–3 mo). However, the addition of 10^{-2} M morphine to these slices dramatically stimulated the uptake of P_i^{32} into phosphatidic acid (303 percent) and triphosphoinositide (370 percent). Morphine-C^{14} levels of 1.21 nmol/g of brain were obtained 1 h later for the tolerant guinea pigs and from 1.10 to 0.10 nmol/g 1 to 10 h after drug in the nontolerant animals. It is concluded that subcutaneously administered morphine stimulates phospholipid metabolism in cortical slices from nontolerant guinea pigs, an adaptation to this effect occurs in the chronically morphine-treated animals and P_i^{32} uptake into polyphosphoinositides from abstinent guinea pigs is markedly enhanced in the presence of added morphine.

370. Mulé, S.J., Redman, C.M., and Flesher, J.W.: Intracellular disposition of H^3-morphine in the brain and liver of nontolerant and tolerant guinea pigs. *The Journal of Pharmacology and Experimental Therapeutics* 157:459–471 (1967).

This study was initiated to ascertain the intracellular localization of H^3-morphine and to determine the effect of both tolerance and nalorphine on the intracellular disposition of this drug. H^3-morphine was prepared by catalytic exchange and was purified, and a specific activity of 9.2 mc/mmol was obtained. A sensitive and specific method for the

estimation of H^3-morphine in the intracellular fractions was utilized. After differential centrifugation the chemical and enzymatic composition of the subcellular fractions were determined. One hour after the s.c. administration of 10 mg/kg (free base) of H^3-morphine, the intracellular localization of the drug was determined in the brain and liver of nontolerant, tolerant, and nalorphine-antagonized guinea pigs. The mean percentage values for the nontolerant guinea-pig brain fractions were: 10 percent crude nuclei; 14 percent crude mitochondria; 6 percent microsomes; 68 percent supernatant; 1 percent subnuclear N_1; 2 percent purified nuclei N_2; in the submitochondrial fractions, 3 percent myelin fragments (A); 1 percent nerve ending fragments with synaptic vesicles (B); 1 percent cholinergic nerve endings (C); 0.2 percent noncholinergic nerve endings (D); 1 percent free mitochondria (E); hypoosmotic shock of the crude mitochrondria, 4 percent swollen mitochondria (M_1); 1 percent synaptic vesicles (M_2); and 8 percent supernatant (M_3). The mean percentage values for the nontolerant guinea-pig liver fractions were: 25 percent crude nuclei; 3 percent purified nuclei; 10 percent mitochrondria; 11 percent microsomal-1; 8 percent microsomal-2; 4 percent smooth microsomes; 3 percent rough microsomes; and 52 percent supernatant. Neither the development of tolerance nor the administration of nalorphine to the nontolerant and tolerant animals altered significantly the subcellular localization of H^3-morphine. It is concluded that morphine was primarily localized in the supernatant fractions of brain and liver as free drug and that neither tolerance nor nalorphine antagonism alters the intracellular disposition of morphine.

371. O'Donnell, J.A.: The rise and decline of a subculture. *Social Problems* 15:73–84 (1967).

It has been suggested by Cohen (1955) that a new subculture arises when it provides a solution to specific problems of adjustment shared among a community of individuals. This concept is tested against, and found to apply to, data on the history of narcotic use in Kentucky, available from a followup study of several hundred narcotic addicts. Before 1914 narcotics could be obtained legally, easily, and cheaply, and there were no signs of a subculture among the addicts in Kentucky. After 1914 drugs could be obtained only with difficulty, but could be obtained through contact with other addicts, and in the 1920's and 1930's a subculture emerged. After 1940 the subculture no longer provided a solution to the problem of obtaining drugs, because illicit channels of supply were blocked, and drugs could be obtained only from physicians, not from addicts. Under these conditions the subculture declined. These conclusions are based on a measure of involvement in the subculture, and the changing associations of other variables, over time, with this measure.

372. O'Donnell, J.A., Besteman, K.J., and Jones, J.P.: Marital history of narcotics addicts. *International Journal of the Addictions* 2:21–38 (1967).

About twice as many as expected of the male subjects never married. The more striking fact about the marital histories, however, is that both men and women had multiple marriages much more often than the base Kentucky population. Marriages were likely to end in divorce or separation. Subjects had only about two-thirds the number of children that would have been expected. Data were collected on four kinds of deviant behavior in the spouses of subjects—narcotics use, alcoholism, prison record, and mental illness. The total number of deviant spouses and the number of user spouses were so much beyond chance expectancy as to establish that some selective factors must have been operating. Five hypotheses were suggested to account for the frequency of narcotics use and other deviance in spouses. Some support was found for all, but in each case the pattern for female subjects was found to differ from that for the males. In general, male subjects showed a slight tendency to select users or otherwise deviant women as wives but a moderately strong tendency to make their wives deviant, especially in the form of narcotics use, after marriage. Female subjects showed a marked tendency to select user or otherwise deviant men as husbands; the nondeviants they married became deviant fairly often, but not users. Male subjects had as many as two deviant wives in very few cases, and multiple marriages increased the probability of having a deviant wife only in proportion to the number of marriages. But women with a deviant husband tended to have more than one, and the men they married were much more likely to be deviant if it was a third or later marriage than if it was a first or second marriage for the woman. With reference to narcotics use in the spouse, those male subjects who had such a wife differed little from those with no user wife. What difference existed seems to have been somewhat greater involvement in a deviant subculture for those with user wives. The female subjects with user husbands, on the other hand, differed markedly from those with no such husband, and the difference is clearly associated with greater involvement in the drug and criminal subcultures. Men involved in a deviant subculture were somewhat more likely than others to choose a deviant woman as wife, but their choice was clearly not restricted to such women, and many married nondeviants. But women involved in the same subculture chose deviant men as husbands so consistently as to suggest that their choice was largely restricted to these men. The data clearly and consistently indicate that the transmission of narcotics use in marriage was from husband to wife much more often than from wife to husband. There is also a suggestion, but no more, that when transmission was from wife to husband this represented a conscious act of making the man an addict, for utilitarian reasons—though in these cases

the man was clearly deviant before his use of narcotics and the use was but a short step further along a familiar road. When transmission was from husband to wife, the drugs were said to be given for illness or pain, with no suggestion of intended benefit for the giver. This difference, however, may establish little more than the readiness of informants to attribute any evil to women who were unmistakably labeled as deviants. Perhaps the more interesting finding is that in most cases where both husband and wife were users, all subjects and other informants insisted that they became users independently, or refrained from assigning the responsibility to one of them. Addicts, more ready than most people to admit to disapproved actions, rarely admit to making an addict of another person.

373. Redman, C.M.: Studies on the transfer of incomplete polypeptide chains across rat liver microsomal membranes in vitro. *Journal of Biological Chemistry* 242:761–768 (1967).

A rat liver microsomal system in vitro was used to study the transport of protein from the attached ribosomes to the contents of the microsomal vesicle. Puromycin caused a release of the protein from the ribosomes and the released protein was transferred to the contents of the microsomal vesicle. The transfer of nascent protein across the microsomal membrane was not accompanied by any changes in phospholipid metabolism and occurred in the absence of adenosine triphosphate and of any added enzyme and also at 0^0. The only requirement needed for transport of the nascent protein across the microsomal membrane is that it be released from the ribosomes.

374. Wikler, A. and Pescor, F.T.: Classical conditioning of a morphine abstinence phenomenon, reinforcement of opioid-drinking behavior and "relapse" in morphine-addicted rats. *Psychopharmacologia* 10:255–284 (1967).

For 6-week periods in two studies, rats made tolerant to and maintained on intraperitoneal injection of morphine (200 mg/kg) once daily in the morning resided on alternate nights in one end of a three compartment linear maze with water for drinking and on the intervening nights in the other end-compartment with etonitazene (10 μg/ml) for drinking. On this schedule, temporal contiguity was provided between the unrelieved nocturnal "primary" morphine abstinence syndrome (including elevated frequency of "wet-dog" shakes) and the specific environment of the water end of the linear maze, while in the other end, opportunity was provided for reinforcement of etonitazene drinking through reduction of the nocturnal "primary" morphine abstinence syndrome. Saline-injected normal rats were trained identically except that the concentration of etonitazene was 5 μg/ml. In one study, the etonitazene solution was tagged with anise flavor while in the other

study, tactile-visual cues were used. Also, other morphine-tolerant and normal rats were maintained on intraperitoneal injections of morphine (200 mg/kg) or saline respectively once each morning for 6 weeks in home cages without any training. At the end of the 6-week periods, all injections were terminated and all rats in linear mazes were transferred to home cages. On test days at intervals of one or more weeks thereafter, the previously morphine-injected rats exhibited higher "wet-dog" shake frequencies in their former "abstinence places" (linear maze or home cage) over periods of 155 and 44 days after termination of injections in the two studies, while conditions of previous housing were not systematically related to "wet-dog" shake frequencies in the previously saline-injected normal rats. In "free choice" tests (etonitazene, 5 μg/kg, versus water) conducted on the nights of the same test days, the previously morphine-injected rats (both studies) drank more of the etonitazene solution than the previously saline-injected normal rats up to 58 days after termination of injections in one study and 44 days in the other, but "trained" and "untrained" previously morphine-injected rats did not differ significantly from each other in this regard. It is concluded that although classical conditioning of morphine-abstinence phenomena (and by inference, "craving" for the drug) is demonstrable, the prepotent factor in disposing to relapse, at least in the rat under the experimental conditions described, is the long-term persistence of unconditioned disturbances in homeostasis following withdrawal of morphine which can provide a source of reinforcement for operant conditioning of opioid-seeking behavior during "relapse-testing" sessions even without benefit of previous "training."

1968

375. Eisenman, A.J., Sloan, J.W., Martin, W.R., Jasinski, D.R., and Brooks, J.W.: Catecholamine and 17-hydroxycorticosteroid excretion during a cycle of morphine dependence in man. *Committee on Problems of Drug Dependence.* Washington, D.C.: National Academy of Sciences, National Research Council, 1968.

Subjects given morphine in ascending doses had significantly more urinary epinephrine and norepinephrine than during the preaddiction period. The excretion of 17–OHCS was decreased, although not significantly, while urinary dopamine, creatinine, and urine volumes were unchanged. During the stabilization period, urinary norepinephrine, on the basis of creatinine excretion, and urine volumes were significantly elevated. Epinephrine, dopamine, 17–OHCS, and creatinine levels did not differ from preaddiction values. When mor-

phine was either gradually reduced or completely withdrawn urinary epinephrine, norepinephrine, and dopamine levels were within the preaddiction range. The excretion of 17–OHCS, based on creatinine, was significantly elevated while urine volume and creatinine values were statistically decreased during both periods. Epinephrine excretion increased after acute withdrawal and was significantly elevated at the 7th and 17th weeks following complete withdrawal. Urine output remained significantly decreased through the seventh week of abstinence. All other parameters were within the preaddiction range by the seventh week of abstinence.

376. Essig, C.F.: Addiction to barbiturate and nonbarbiturate sedative drugs. In: Wikler, A. (ed): *The Addictive States,* Vol. 46, pp. 188–198, Research Publications, Association for Research in Nervous and Mental Disease. Baltimore: Williams and Wilkins, 1968.

If abused, the barbiturates and eight of the newer nonbarbiturate sedative-hypnotic drugs have been reported to cause states of intoxication similar to that associated with excessive use of alcohol. These drugs are meprobamate, glutethimide, ethchlorvynol, ethinamate, methyprylon, chlordiazepoxide, diazepam, and oxazepam. Excessive use of these drugs can cause drowsiness, difficulty in thinking, and incoordination of movement. Such behavioral impairments are conducive to vehicular accidents, falling, assaultive behavior, and interference with occupational skills. The chronic abuse of barbiturates, meprobamate, glutethimide, ethinamate, ethchlorvynol, methyprylon, chlordiazepoxide, or diazepam can cause physical dependence. After any of these drugs has been abused, abrupt withdrawal can result in a potentially serious withdrawal syndrome. The major abstinence manifestations are generalized convulsions, a delirium or both. Death has been attributed to the withdrawal of a barbiturate, meprobamate, and methyprylon. The abuse of these drugs can cause harm to the user or society, and they are considered to be drugs of addiction. Caution is indicated in prescribing them in order to prevent their abuse.

377. Essig, C.F.: The effect of an anticonvulsant on the seizure threshold elevation caused by repeated electroconvulsions. *Archives Internationales de Pharmacodynamie et de Therapie* 173:189–194 (1968).

In cats the threshold for electroconvulsions increases if such seizures are induced every day. The effect of sodium barbital on this phenomenon was tested. Cats that received electroconvulsions without barbital developed an increase in seizure threshold of 3.0 ± 1.3 (S.E.) mA. Cats that received 30 mg/kg/day of barbital and daily electroconvulsions acquired an elevation in threshold of 6.8±2.4 mA. It is interesting that an anticonvulsant drug capable of increasing the seizure threshold did not inhibit the elevation caused by repeated electroconvulsions.

378. Essig, C.F.: Increased water consumption following forced drinking of alcohol in rats. *Psychopharmacologia* 12:333–337 (1968).

An attempt was made to induce physical dependence in rats by restricting their fluid intake to concentrations of alcohol that were increased from 5–20 percent during 4 months. Alcohol intake decreased during the month that the 20 percent concentration was available. Following alcohol withdrawal water was consumed in significantly greater amounts than in control rats on the 1st and 4th through 12th days thereafter. It is doubtful that this was due to abstinence. A fluid deficit might have developed during the last month on alcohol so that an increase in water consumption occurred when it became available.

379. Essig, C.F.: Possible relation of brain gamma-aminobutyric acid (GABA) to barbiturate abstinence convulsions. *Archives Internationales de Pharmacodynamie et de Therapie* 176:97–103 (1968).

The effect of amino-oxyacetic acid (AOAA) on sodium barbital withdrawal convulsions was tested in white rats. AOAA was given every 8 hours at 15 and 30 mg/kg dose levels during the first 65 hours of barbital withdrawal. The drug prevented abstinence convulsions in 75 and 100 percent of the low and high dosage groups respectively. Convulsions occurred in some rats from 24 and 63 hours after the AOAA was discontinued. The possible mechanisms underlying the anticonvulsant effect of AOAA were discussed. The drug induces an accumulation of brain gamma-aminobutyric acid (GABA) in normal rats. To establish that this is its mode of anticonvulsant action, direct measures of brain GABA will have to be done in rats that have undergone barbiturate intoxication and withdrawal.

380. Essig, C.F. and Lam, R.C.: Convulsions and hallucinatory behavior following alcohol withdrawal in the dog. *Archives of Neurology* 18:626–632 (1968).

In order to produce an animal model of the alcohol withdrawal syndrome alcohol (ethanol) was administered to beagle dogs by means of a gastric cannula. Four of 12 dogs died between the 10th and 39th days of chronic intoxication. Two of these dogs had developed duodenal mucosal ulcerations, and all of them had petechial hemorrhagic foci in the mucosa of the intestinal tract. None of the dogs were observed to have convulsions or hallucinatory behavior during 54 days of chronic alcoholic intoxication. After the alcohol was withdrawn, five of eight dogs (62.5 percent) developed one to three convulsions between the 11th and 48th hours of abstinence. Hallucinatory behavior occurred in another dog, and four dogs died during withdrawal. Other abstinence manifestations were as follows: trembling, anorexia, weight loss, and polydipsia. It is concluded that alcohol can produce physical depen-

dence in dogs. Such dependence can result in an abstinence syndrome not unlike alcoholic delirium tremens in man. The canine model of delirium tremens might be useful in assaying the effectiveness of various drugs in the treatment of this condition in man.

381. Gorodetzky, C.W., Sapira, J.D., Jasinski, D.R., and Martin, W.R.: Liver disease in narcotic addicts. I. The role of the drug. *Clinical Pharmacology and Therapeutics* 9:720–724 (1968).

Earlier studies often quoted in support of a direct hepatotoxic effect of single doses of opiates are inconclusive on the basis of the use of outmoded measures of liver function and inadequacies of experimental design. More recently, Brooks and colleagues reported the effect on liver function of long-term morphine administration in rhesus monkeys. They found that the addicted group had a higher mean SGOT than the control group, but lower mean levels of SGPT and ICD (isocitric dehydrogenase). A number of other measures showed no difference between addicted and control groups. They concluded that abnormal liver function tests of opiate addicts were probably not due to a hepatotoxic effect of the opiates. The results of the present study in man support the general conclusion of Brooks and colleagues. No significant changes were found in mean levels of SGOT, SGPT, or TT, or in the relative incidence of abnormal CF determinations during a 7- to 9-month period of addiction to morphine. Although all but one of the subjects had at least one abnormal liver function test, the occurrence of these abnormalities did not follow any pattern and appeared to have no relation to the administration of morphine. Levine and Payne found a similar lack of correlation between self-administration of heroin and SGOT levels in several patients in a group of opiate addicts. These investigators also found that 14 of the 21 addicts followed over a period of 10 months while taking heroin "on the street" had some abnormality in SGOT levels. Similarly, in our study, 14 of 20 subjects showed at least one elevation in transaminase level. Levine and Payne noted that the SGOT levels fluctuated during the followup period, sometimes being normal and sometimes increased, although the subjects persisted in taking drugs throughout this period. Marks and Chapple followed a group of 89 heroin and cocaine users in England and found abnormal liver function in 80 percent. They state that occasionally a sudden rise in transaminase levels was associated with a relapse to heroin and cocaine use; in some cases, very high transaminase levels returned to normal 2 to 3 weeks following hospital admission (presumably with attendant withdrawal of opiates, although this is not stated). In addition, these authors feel that a certain pattern of abnormal liver function, including elevated transaminase levels, may be a valuable adjunct in recognizing and diagnosing heroin and cocaine use; and, thus, a sudden rise in transaminase

may be one of the earliest signs of relapse. The present study was performed with the use of uncontaminated morphine solution, administered subcutaneously with sterile technique (compared with the English study where addicts took heroin and cocaine "on the street") and does not support the conclusions of Marks and Chapple. Six of the 20 subjects did not show any abnormality in transaminase levels during the course of addiction; of the 14 who did show transaminase elevations, there was no pattern indicating a rise on initiation of morphine administration or during any given period of the addiction cycle. In addition, the data of Levine and Payne show 7 of 21 addicts with no abnormalities of transaminase, although these subjects continued to take heroin on the street. The present study clearly shows that long-term morphine administration per se is not associated with the development of abnormal liver function. It is concluded that the high incidence of abnormal liver function observed in morphine and heroin addicts probably is not due to a direct hepatotoxic effect of the opiate.

382. Haertzen, C.A., Hill, H.E., and Monroe, J.J.: MMPI scales for differentiating and predicting relapse in alcoholics, opiate addicts, and criminals. *International Journal of the Addictions* 3:91–106 (1968).

An alcoholic versus addict (AAF) differentiating key was developed from items in the short form of the MMPI. A small but significant difference was found between alcoholics and addicts on the scale after it was corrected for the first two individual difference factors of the MMPI. The scale, scored in the direction of alcoholics, was negatively correlated with time after admission to the hospital (index of withdrawal) in both alcoholics and addicts. Scores were related to severity of addiction in addicts and recidivism in criminals. An antisocial scale (Ant) was developed by correlating MMPI items with a social maladaptation factor identified previously by Astin and Monroe. This scale, corrected for the first two MMPI individual difference factors, was correlated with relapse to the use of narcotics and criminal recidivism. Neither scale was predictive of relapse to alcohol.

383. Haertzen, C.A. and Hooks, N.T., Jr.: Effects of adaptation level, context and face validity on responses to self-report psychological inventories. *Psychological Record* 18:339–349 (1968).

The adaptation level or contrast and context effects as conceived by Helson on self-report questionnaires was investigated using the Addiction Research Center Inventory, MMPI, and CPI on overlapping items. The absence of contrast or context effects suggests that the point of reference or determinant for a response to a self-report or personality question for a group is determined by the item itself and is unaffected by adjacent items or by items as a whole. Significant individual differences

were found for a contrast tendency, indexed by scoring reversals of responses to adjacent items, irrespective of the selection of adjacent items, but the generality of the reversal tendency, as evaluated by correlations across tests, was a function of the degree of dissimilarity of adjacent items. The reversal tendency based on a change of response to dissimilar items accounts for as much variation across tests as social desirability or response set. These tendencies appear to be overestimated in each test, since they account for much more variation within tests than across tests.

384. Haertzen, C.A. and Meketon, M.J.: Opiate withdrawal as measured by the Addiction Research Center Inventory (ARCI). *Diseases of the Nervous System* 29:450–455 (1968).

Opiate addicts (N=102) were given the ARCI approximately 10 days after admission to the NIMH Clinical Research Center. An opiate withdrawal scale (OPWL) was developed by comparing responses of 42 subjects who were subjectively experiencing withdrawal with those of 60 who were not. Scores on the scale were highly correlated with having received or not received methadone treatment for withdrawal and were also correlated with time after withdrawal in another group of subjects who had been experimentally addicted to heroin. Opiate and alcohol withdrawal scales are highly correlated indicating that the individual reaction tendencies measured by the scale are similar. However, the correlation between the pattern of effects of opiate and alcohol withdrawal on ARCI items is much lower and suggests that these subjective states are differentiable.

385. Haertzen, C.A., Monroe, J.J., Fuller, G.B., and Sharp, H.: Nonsignificance of membership in Alcoholics Anonymous in hospitalized alcoholics. *Journal of Clinical Psychology* 24:99–103 (1968).

A number of investigators of alcoholics, such as Pattison and Smart, have questioned whether members of Alcoholics Anonymous constitute a representative sample of alcoholics. The work of Trice, especially, suggests that AA members are not representative. In the present study, members and nonmembers of AA in a hospital setting were compared on the Addiction Research Center Inventory (ARCI) and Inventory of Habits and Attitudes (IHA). Both tests measure personality and adjustment characteristics, but the former test is a sensitive measure of subjective experience associated with drugs and alcohol withdrawal, whereas the IHA test gives an indication of the history of alcohol use, functional utility of alcohol, environmental press for using alcohol, and acceptability for therapy. In studies of these tests involving over 700 Ss, AA membership was not a significant determinant of individual differences in response.

386. Hill, H.E., Haertzen, C.A., and Yamahiro, R.S.: The addict physician: a Minnesota Multiphasic Personality Inventory study of the interaction of personality characteristics and availability of narcotics. In: Wikler, A. (ed.): *The Addictive States*, Vol. 46, pp. 321–332, Research Publications, Association for Research in Nervous and Mental Disease. Baltimore: Williams and Wilkins, 1968.

Addict physicians were compared with nonaddict physicians and with unselected white hospitalized addicts on the Minnesota Multiphasic Personality Inventory (MMPI). An inverse relationship was found between deviant personality scores and assumed degree of availability of narcotics. Nonaddict physicians scored well within the normal range on this standard test. In contrast, the addict physicians were significantly higher on nearly all scales and showed neuroticism and considerable indications of maladjustment. The general addict presented much more specificity and significantly greater deviation on nearly all scales than the addict physicians. The possibility was considered that personality deviation may increase in importance in the addiction process as legal or quasi-legal availability of narcotics becomes less. The significance of psychopathic deviation was discussed, as was the background literature.

387. Jasinski, D.R., Martin, W.R., and Sapira, J.D.: Antagonism of the subjective, behavioral, pupillary, and respiratory depressant effects of cyclazocine by naloxone. *Clinical Pharmacology and Therapeutics* 9:215–222 (1968).

Naloxone is an opioid antagonist with little, if any, agonistic activity. Cyclazocine, on the other hand, in addition to antagonizing the effects of morphine, produces agonistic effects in man, some of which resemble the effects produced by morphine and some of which do not. The interaction between naloxone and cyclazocine was assessed in eight subjects. Naloxone antagonized the miotic and respiratory depressant as well as the behavioral and subjective effects of cyclazocine.

388. Jasinski, D.R., Martin, W.R., and Sapira, J.D.: Progress report on the dependence-producing properties of GPA–1657, profadol hydrochloride (CI–572), propiram fumarate (BAY–4503), and dexoxadrol. *Committee on Problems of Drug Dependence.* Washington, D.C.: National Academy of Sciences, National Research Council, 1968.

GPA–1657, profadol, and propiram are analgesics which did not suppress but rather exacerbated morphine abstinence in the monkey thus appearing to act as a narcotic antagonist. In man, studies were conducted to determine if these compounds produce agonist effects which resembled those of morphine or those of nalorphine. GPA–1657 was a typical morphinelike agent in man which did not precipitate abstinence. Profadol was a morphinelike agonist which precipitated

abstinence and was 1/40th to 1/50th as potent as nalorphine. An 80-mg dose of pentazocine also precipitated abstinence. Preliminary observations indicated that propiram also precipitated abstinence. Dexoxadrol in single doses did not produce morphinelike subjective effects or miosis but was a euphoriant, as evidenced by increases on the MBG and the subjects' liking scale. In addition, dexoxadrol produced sedation and psychotomimetic effects. Dexoxadrol did not precipitate abstinence in morphine-dependent subjects.

389. Jones, B.E. and Ayres, J.J.B.: Effects of morphine on differentially conditioned electrodermal responses. In: Wikler, A. (ed.): *The Addictive States*, Vol. 46, pp. 166–175, Research Publications, Association for Research in Nervous and Mental Disease. Baltimore: Williams and Wilkins, 1968.

The effect of morphine sulfate (16 mg/70 kg, i.m.) on retention of differentially conditioned electrodermal responses was studied in eight men. Two tones were used as the differentially conditioned stimuli, and electric shock applied to the fingers was the unconditioned stimulus paired with one of the tones. In comparison with placebo, morphine did not change the amplitude of the orienting or conditioned response to the conditioned tone. Morphine did increase significantly the amplitude of the conditioned response to the unconditioned tone.

390. Martin, W.R.: The basis and possible utility of the use of opioid antagonists in the ambulatory treatment of the addict. In: Wikler, A. (ed.): *The Addictive States,* Vol. 46, pp. 367–377, Research Publications, Association for Research in Nervous and Mental Disease. Baltimore: Williams and Wilkins, 1968.

The theory of the utility of narcotic antagonists in treatment and the pharmacology of cyclazocine are briefly reviewed.

391. Martin, W.R.: A homeostatic and redundancy theory of tolerance to and dependence on narcotic analgesics. In: Wikler, A. (ed.): *The Addictive States,* Vol. 46, pp. 206–225, Research Publications, Association for Research in Nervous and Mental Disease. Baltimore: Williams and Wilkins, 1968.

A homeostatic theory of tolerance and dependence has been presented which offers an explanation for certain signs of morphine action to which acute tolerance develops. In addition, it provides an explanation for certain signs of precipitated abstinence in the acutely dependent animal, as well as for some of the intense phasic changes seen in precipitated abstinence in the chronically dependent subject. As a consequence of chronic morphine administration, another type of tolerance develops, as well as marked changes in the abstinent level of homeostatic

regulation and an increase in the abstinent level of excitability of other neuronal circuits not involved in homeostatic regulation. To explain these phenomena, a redundancy theory of tolerance and dependence has also been presented which postulates parallel pathways mediating physiological responses that differ in their vulnerability to toxins. Although a redundant pathway is necessary for the development of tolerance and dependence, according to the hypothesis, it is not sufficient. It is also necessary for a negative feedback pathway to exist and signal the redundant pathway to hypertrophy in the presence of decreased output of the total pathway.

392. Martin, W.R. and Eades, C.G.: Interactions between norepinephrine antagonists and potentiators (chlorpromazine, chlorpromazine sulfoxide and imipramine) and sympathetic amines (amphetamine and methoxamine) on the flexor reflex of the chronic spinal dog. *International Journal of Neuropharmacology* 7:493–501 (1968).

The interactions of chlorpromazine (5 mg/kg), chlorpromazine sulfoxide (5 mg/kg), or imipramine (0.5 mg/kg), agents which have both adrenergic-blocking and adrenergic-potentiating properties, with amphetamine (2 mg/kg) or methoxamine (0.88 mg/kg), indirectly and directly acting sympathetic amines, were studied on the flexor reflex of the chronic spinal dog. Both methoxamine and *d*-amphetamine facilitate the flexor reflex. Chlorpromazine completely antagonized the facilitatory effects of both methoxamine and *d*-amphetamine. Chlorpromazine sulfoxide and imipramine partially antagonized the facilitatory action of methoxamine; however, the antagonism was surmounted. Neither chlorpromazine sulfoxide nor imipramine antagonized the facilitatory effect of amphetamine; in fact, it was somewhat enhanced by chlorpromazine sulfoxide. It has been concluded that the central adrenergic-blocking property of chlorpromazine predominates, whereas, the adrenergic-blocking and adrenergic-potentiating effects of chlorpromazine sulfoxide and imipramine counterbalance each other.

393. Martin, W.R., Jasinski, D.R., Sapira, J.D., Flanary, H.G., Kelly, O.A., Thompson, A.K., and Logan, C.R.: The respiratory effects of morphine during a cycle of dependence. *The Journal of Pharmacology and Experimental Therapeutics* 162:182–189 (1968).

The responsiveness of the respiratory center to carbon dioxide was studied through a cycle of morphine dependence in seven subjects. During chronic intoxication with morphine, both respiratory rate and the responsiveness of the respiratory center to CO_2 were depressed for over 8 h after each stabilization dose; however, in the morphine-stabilized patients large additional doses of morphine produced only a liminal degree of additional depression. When subjects were withdrawn

from morphine for 16 to 20 h, the sensitivity of the respiratory center to CO_2 was found to be markedly increased above the preaddiction level. The sensitivity of the respiratory center to CO_2 returned to control level within 7 weeks after withdrawal and subsequently the respiratory center was found to be hyposensitive to CO_2. This hyposensitivity persisted through the 30th week. These data indicate that dependence on morphine produces both an early (primary) and protracted (secondary) abstinence syndrome in man. Further, they are consistent with the homeostatic and redundancy theory of physical dependence.

394. Martin, W.R. and Sloan, J.W.: The pathophysiology of morphine dependence and its treatment with opioid antagonists. *Pharmakopsychiatrie Neuro-Psychopharmakologie* 1:260–270 (1968).

The general pathophysiology of narcotic addiction has been discussed. Both animals and man when chronically intoxicated with morphine, and presumably other opioids, have physiological abnormalities that persist throughout the period of intoxication with no appreciable degree of tolerance developing. Some of these persisting changes are an elevation in blood pressure, pulse rate and body temperature, constriction of pupils, and chronic depression of the respiratory system. Associated with these physiological changes are behavioral alterations. Patients chronically intoxicated with narcotics are hypochondriacal and lethargic and lack motivation. The abstinence syndrome in both man and the rat has two phases. The first phase (primary or early abstinence) lasts in the rat approximately 4 or 5 days and is followed by a different phase (secondary or protracted abstinence) which may last up to 6 months. In man, the early abstinence syndrome lasts approximately 1 or 2 months, at which time the protracted abstinence syndrome becomes manifest. It persists for at least 6 months and consists of decreased blood pressure, pulse rate, body temperature, pupillary diameter, and sensitivity of the respiratory center to carbon dioxide. In the rat, protracted abstinence is associated with increased drug-taking behavior. In addition to discussing the importance of protracted abstinence in relapse, the possible role of conditioned abstinence and conditioned drug-seeking behavior has also been discussed, as well as the rationale for using narcotic antagonists in the treatment of the ambulatory narcotic addict. The view has been presented that the chronic administration of narcotic antagonists would prevent the exacerbation of protracted abstinence and may provide a circumstance whereby conditioned abstinence and conditioned drug-seeking behavior could be extinguished.

395. Mulé, S.J.: Effect of morphine and nalorphine or brain phospholipid metabolism. In: Wikler, A. (ed.): *The Addictive States,* Vol. 46,

pp. 32–52, Research Publications, Association for Research in Nervous and Mental Disease. Baltimore: Williams and Wilkins, 1968.

The results of these studies show that morphine and nalorphine markedly alter phospholipid metabolism in brain tissue. A significant stimulation in the incorporation of P_i^{32} into phosphatidylinositol, phosphatidylserine, phosphatidylethanolamine, phosphatidic acid, and diphosphoinositide of 34 to 299 percent was achieved with in vitro levels of 10^{-2} to 10^{-3} M morphine and nalorphine. A significant stimulation of 24 to 83 percent was still evident for certain phosphatides in the presence of 10^{-6} M morphine or nalorphine. Concentrations of nalorphine (10^{-2} to 10^{-6} M) did not consistently alter the effect of 10^{-2} M morphine on phospholipid metabolism. The data obtained with the C^{14}-labeled precursors were quite similar to that observed with P_i^{32}, indicating the turnover of the entire phosphatide molecule in vitro. These results suggest that D-1,2-diglyceride, an essential intermediate in the biosynthesis of glycerophosphatides, becomes limiting. Studies on the effect of in vivo levels of morphine following a 40 mg/kg injection of morphine demonstrated a significant stimulation (49 to 115 percent) of the incorporation of P_i^{32} into the phospholipids with cortical slices from nontolerant animals sacrificed at 1 hour. A variable effect was obtained with slices obtained from animals sacrificed at 4 hours and no effect observed 10 hours after drug in the nontolerant guinea pig. The phospholipid effect seemed to parallel the levels of morphine in the CNS. No effect on phospholipid metabolism was obtained with cerebral cortex slices incubated without additional morphine from chronically morphine-treated animals. The addition of 10^{-2} to 10^{-6} M morphine to these slices seemed to produce less of an effect on the incorporation of P_i^{32} into phosphatides than that observed with nontolerant animals. No effect on phospholipid metabolism occurred with slices from abstinent guinea pigs (24 hours to 3 months). However, the addition of 10^{-2} M morphine to these slices dramatically stimulated the uptake of P_i^{32} into phosphatidic acid (303 percent) and triphosphoinositide (370 percent). Morphine inhibits phospholipid-facilitated Ca^{++} transport, and the displacement of Ca^{++} from the anionic binding sites of the phosphatides may be directly involved in the morphine effect on phospholipid metabolism.

396. Mulé, S.J., Clements, T.H., and Gorodetzky, C.W.: The metabolic fate of H^3-cyclazocine in dogs. *The Journal of Pharmacology and Experimental Therapeutics* 160:387–396 (1968).

The metabolism of H^3-cyclazocine was studied in nontolerant, tolerant, and abstinent dogs after a 1.25 mg/kg (free base) s.c. injection of the drug. Norcyclazocine and cyclazocine were identified in the urine of these dogs after extraction and direct application of hydrolyzed and

unhydrolyzed urine samples to chromatographic paper buffered with 0.1 M phosphate or impregnated with silicic acid. The chromatograms were developed with *tert*.-amyl alcohol-*n*-butyl ether-water (80:7:13, v/v) or ethyl acetate-methanol-NH_4OH (85:10:5, v/v). A method was developed for the estimation of H^3-norcyclazocine in biologic material with a minimal sensitivity of 5 ng/ml. In the urine of nontolerant, tolerant, and abstinent dogs, 2.3 to 2.7 percent of the H^3-cyclazocine was recovered as free norcyclazocine and an equal amount as conjugated norcyclazocine. In the feces of these dogs, from 1.5 to 2.4 percent of the free and 0.02 to 0.7 percent of the conjugated norcyclazocine was obtained. Norcyclazocine was not found in the brain of the dogs at various time intervals, but the metabolite was obtained in peripheral tissues. Urine samples were subjected to acid and enzymatic hydrolysis, using β-glucuronidase and phenol sulfatase. The data indicated that the conjugate of both cyclazocine and norcyclazocine was a glucuronide. Norcyclazocine (1.0 mg/kg) did not significantly depress the flexor reflex of the chronic spinal dog. It is concluded that norcyclazocine is not an active metabolite of cyclazocine and that 47 to 66 percent of the administered H^3-cyclazocine was accounted for as free and conjugated cyclazocine and norcyclazocine, as determined over a 5-day period.

397. Mulé, S.J., Clements, T.H., Layson, R.C., and Haertzen, C.A.: Analgesia in guinea pigs: a measure of tolerance development. *Archives Internationales de Pharmacodynamie et de Therapie* 173:201–212 (1968).

The thermal stimulating apparatus was relatively easy to construct, and permitted the determination of pain thresholds in animals rapidly and quantitatively. Peak analgesia occurred at about 1.5 hours after a 10 mg/kg (free base) subcutaneous injection of morphine and lasted through 5 hours in the nontolerant guinea pigs. Peak brain levels of morphine-^{14}C occurred at 30 minutes (70 ng/gm) after a 10 mg/kg (free base) subcutaneous injection of labeled drug in the nontolerant guinea pig and dropped rapidly to a level of 15 ng/gm at 8 hours. Tolerance to the analgesic effect of morphine was achieved in guinea pigs after the administration of 10 mg/kg per 8 hours for a period of 34 to 36 days. The levels of morphine-^{14}C in the brain of tolerant (34 to 36 days) guinea pigs ranged between 80 and 90 ng/g for the first 2 hours then dropped rapidly to a level of 8 ng/g at 8 hours. A good correlation between the analgesic response to morphine and the brain levels of the drug did not appear to exist.

398. O'Donnell, J.A.: Social factors and follow-up studies in opioid addiction. In: Wikler, A. (ed.): *The Addictive States,* Vol. 46, pp. 333–346, Research Publications, Association for Research in Nervous and Mental Disease. Baltimore: Williams and Wilkins, 1968.

There is much evidence, especially in the fact that centers of addiction are areas of poverty, crime, and other social problems, populated by minority groups, that social factors are important in addiction, but we do not know how they operate. Similarly, psychological explanations tend to be post hoc, and do not enable us to predict. There have been too few studies which combine social and psychological variables, which include nonusers and nonaddicts, and which focus on the roads to and out of addiction. While the early stages of the addiction process remain unclear, followup studies in recent years have produced some knowledge about later stages. While it is true that addicts tend to relapse, it is equally true that abstinence increases with time. In a Kentucky followup, a major reason for this was the increased difficulty of obtaining narcotics, attributable in part to law enforcement agencies but even more to improving standards of medical practice. The evidence suggests that present policies have succeeded in reducing one pattern of addiction—the old "Southern White" pattern—though not the more recent metropolitan pattern. The findings of followup studies suggest that treatment effectiveness cannot be evaluated against an implied assumption of zero abstinence in the absence of treatment, but only against appropriate control groups or base expectancy rates.

399. Sapira, J.D.: The determination of urinary 3-methoxy-4-hydroxy-mandelic acid and free 3-methoxy-4-hydroxy-phenylglycol. *Clinica Chimica Acta* 20:139–145 (1968).

Both free 3-methoxy-4-hydroxy-phenylglycol and 3-methoxy-4-hydroxy-mandelic acid are extracted into ethyl acetate at highly acid pH. Free 3-methoxy-4-hydroxy-phenylglycol, but not 3-methoxy-4-hydroxy-mandelic acid, can be extracted into ethyl acetate at pH 6.2. This allows free MHPG to be determined separately and permits calculation of the true quantity of VMA in the highly acidic extract.

400. Sapira, J.D.: The narcotic addict as a medical patient. *American Journal of Medicine* 45:555–588 (1968).

Narcotic addicts present with many physical findings and disease patterns that are relatively unusual. These are discussed in a systematic fashion with emphasis on pathophysiologic explanations when available. Many obscure issues could profitably be investigated (or reinvestigated) with the use of modern technics of clinical research.

401. Sapira, J.D., Jasinski, D.R., and Gorodetzky, C.W.: Liver disease in narcotic addicts. II. The role of the needle. *Clinical Pharmacology and Therapeutics* 9:725–739 (1968).

A liver disease is described among narcotic addicts examined at the Addiction Research Center. The clinical picture is described and dis-

cussed in light of the pertinent literature. It is suggested that many narcotic addicts have a long-term intermittent serum hepatitis, chronic addiction serum hepatitis. There is a correlation between evidences of this liver disease and the duration of exposure to hypodermic equipment.

402. Sloan, J.W. and Eisenman, A.J.: Long persisting changes in catecholamine metabolism following addiction to and withdrawal from morphine. In: Wikler, A. (ed.): *The Addictive States,* Vol. 46, pp. 96–105, Research Publications, Association for Research in Nervous and Mental Disease. Baltimore: Williams and Wilkins, 1968.

The effects of chronic morphine intoxication and protracted abstinence on rat urinary catecholamine levels were studied with particular interest in the consequences of long-term abstinence. In addition, weights and catecholamine levels were determined in brain and adrenal glands 5 months after the last injection of morphine. During addiction the mean excretion of the urinary catecholamines was significantly higher in the addicted than in the control rats. During early abstinence epinephrine excretion increased and reached a maximum within 48 hours. Norepinephrine and dopamine excretion was maximal on the third day of abstinence, at a time when the epinephrine output was rapidly declining. By the end of 2 weeks, urinary catecholamine values were normal or subnormal. Epinephrine and dopamine excretion in the morphine-abstinent rats did not vary significantly from controls throughout the protracted abstinence period. Urinary norepinephrine, on the other hand, fell below control levels and remained subnormal consistently during this long-term period. Brain weights were unchanged and brain norepinephrine tended to be higher and dopamine lower in the test animals. The adrenal glands of the treated rats were significantly hypertrophied, contained significantly more norepinephrine and tended to have higher epinephrine values than controls.

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403. Christian, S.T., Gorodetzky, C.W., and Lewis, D.V.: Structure activity relationships of normeperidine congeners on *in vitro* cholinesterase systems and *in vivo* analgesia. *Committee on Problems of Drug Depen-* (eds.): *Abuse of Central Stimulants,* pp. 89–112. Stockholm: Almqvist and Wiksell, 1969.

404. Christian, S.T. and Janetzko, R.: The interaction of the fluorescent dye 1-anilino-8-napthalene sulfonic acid with horse serum

butyrylcholinesterase. *Biochemical and Biophysical Research Communication* 37:1022–1027 (1969).

The binding of 1-anilino-8-naphthalene sulfonic acid (ANS) to horse serum butyrylcholinesterase is accompanied by a marked increase in the fluorescence quantum yield of the dye. When the ANS ligand binds to the enzyme in the presence of acetylcholine an apparent "uncompetitive" mode of inhibition is demonstrated. This type of inhibition may, however, be artifactual since the ANS molecule will also bind to the enzyme in the absence of substrate. Binding of the dye to the protein has been characterized by fluorescent titrations and by fluorescence polarization.

405. Eisenman, A.J., Sloan, J.W., Martin, W.R., Jasinski, D.R., and Brooks, J.W.: Catecholamine and 17-hydroxycorticosteroid excretion during a cycle of morphine dependence in man. *Journal of Psychiatric Research* 7:19–28 (1969).

Subjects given morphine in ascending doses had significantly more urinary epinephrine and norepinephrine than during the preaddiction period. The excretion of 17–OHCS was decreased, although not significantly, while urinary dopamine, creatinine, and urine volume were unchanged. During the stabilization period, urinary norepinephrine, on the basis of creatinine excretion, and urine volumes were significantly elevated. Epinephrine, dopamine, 17–OHCS, and creatinine levels did not differ from preaddiction values. When morphine was either gradually reduced or completely withdrawn urinary epinephrine, norepinephrine, and dopamine levels were within the preaddiction range. The excretion of 17–OHCS, based on creatinine, was significantly elevated while urine volume and creatinine values were statistically decreased during both periods. Epinephrine excretion increased after acute withdrawal and was significantly elevated at the 7th and 17th weeks following complete withdrawal. Urine output remained significantly decreased through the seventh week of abstinence. All other parameters were within the preaddiction range by the seventh week of abstinence.

406. Essig, C.F.: The potential risk of addiction to nonbarbiturate sedative and minor tranquilizing drugs. In: Sjoqvist, F. and Tottie, M. (eds.): *Abuse of Central Stimulants,* pp. 89–112. Stockholm: Almqvist and Wiksell, 1969.

407. Essig, C.F., Jones, B.E., and Lam, R.C.: The effect of pentobarbital on alcohol withdrawal in dogs. *Archives of Neurology* 20:554–558 (1969).

Pentobarbital was administered to dogs in order to determine

whether it would prevent the major abstinence manifestations of alcohol withdrawal under controlled conditions. The drug was given to five dogs in decreasing doses during the first 8 days of alcohol withdrawal. Pentobarbital suppressed withdrawal tremulousness and prevented abstinence convulsions in all cases. None of the treated dogs died as a result of alcohol withdrawal. Four of the six dogs which received no treatment during alcohol withdrawal had either one or two major abstinence convulsions. Four of the untreated dogs died during alcohol withdrawal. Pentobarbital is an effective treatment for canine delirium tremens. The clinical implications of this observation are discussed.

408. Gorodetzky, C.W. and Thompson, W.O.: A statistical approach to the analysis of dose response curves for drug receptor interaction. *Committee on Problems of Drug Dependence.* Washington, D.C.: National Academy of Sciences, National Research Council, 1969.

A statistical method is presented to determine the value of the constants which best fit a set of dose-response data to a hypothesized receptor model, formulated according to "drug occupancy theory." The method involves expansion of the model in a Taylor series and iterating to determine the value of the constants which minimize the error sum of squares. An analysis of variance is then performed which identifies variance contributions due to presence of the hypothesized model, lack of fit of the hypothesized model to the true model, and other classically identifiable variance components depending on the particular experimental design. The lack of fit mean squares for different hypothesized models allow comparison among the models for the relative degree to which they fit the true model. A numerical example is presented showing evaluation of a set of dose-response data for best fit to a hypothesized one drug, one receptor model.

409. Haertzen, C.A.: Contrast effect on subjective experience in drug experiments. *Psychological Reports* 24:69–70 (1969).

Contrast effects in an experiment involving no-drug, placebo, and seven drugs were postulated on the basis of Helson's adaptation level theory. For 250 male opiate addicts, it was expected and found that general subjective experiences peculiar to drugs were smaller for no-drug or placebo conditions when these conditions were administered after rather than before potent drugs such as morphine or LSD.

410. Haertzen, C.A.: Implications of Eysenck's criterion analysis for test construction: Is the MMPI schizophrenia scale a criterion for schizophrenia? *Psychological Reports* 24:894 (1969).

A scale meets the requirement for criterion analysis (CAR) as interpreted from the work of Eysenck (1950) if the correlations of items with

a scale predict the direction and quantity of differences between appropriate criterion groups on the same items. To test whether the MMPI Sc scale meets CAR, the Sc scale was correlated (tetrachoric) with a set of 550 items that stress immediate subjective experiences using a cross-sectional sample of 94 male and 113 female mentally ill Ss from the Minn. St. Peter State Hospital tested by R. Long and P. Philip (Haertzen and Panton, 1967). These correlations failed to predict questions which differentiated schizophrenics from other classes of mentally ill Ss. The differences between the entire mentally ill group and a normal college group of 83 male and 132 female Ss tested by S. Grupp of the Illinois State University and W. Johnson of Morningside College, Iowa (Haertzen and Panton, 1967) were negatively rather than positively correlated with Sc. These results suggest that Sc fails to meet CAR. Studies with other tests indicate that CAR is difficult to meet (Haertzen and Horine, 1966). An extended version of this paper shows how scales can be developed which neutralize and use the nuisance variance in a scale or which maximize the possibility of meeting CAR.

411. Haertzen, C.A. and Hooks, N.T., Jr.: Changes in personality and subjective experience associated with the chronic administration and withdrawal of opiates. *Journal of Nervous and Mental Disease* 148:606–614 (1969).

Fifteen opiate addicts were followed over an addiction cycle at the Addiction Research Center, Lexington, Ky., and were tested with the Minnesota Multiphasic Personality Inventory (MMPI), Addiction Research Center Inventory, Personal Inventory, and an appetite rating scale: (1) prior to drug administration, (2) after 3.5 months of chronic administration of morphine or heroin when they had been stabilized on the equivalent of 240 mg of morphine per day, and (3) on the 10th day of dose reduction. Euphoria, which was increased after an acute dose of morphine, was reduced to predrug levels during chronic administration, but tolerance failed to develop completely to such symptoms as lowered motivation for activity, constipation, dryness of the skin, and appetite for the opiate drug used in the experiment. On the other hand, hypochondriasis (MMPI) increased during the chronic phase but was not evident after a single dose of morphine. Psychopathic traits, believed by many to be exaggerated by opiates, were not increased during acute, chronic, or withdrawal phases of the addiction cycle. Many other traits, interestingly, such as acceptability for psychotherapy, were not altered. During withdrawal, neurotic traits such as depression, hypochondriasis, anxiety, and feelings of weakness, sickness, and irritability, as well as classically defined withdrawal symptoms were markedly increased. The immediate subjective feeling of usefulness of morphine or heroin for

settling symptoms was more highly correlated with the intensity of opiate withdrawal symptoms than with psychopathic traits.

412. Haertzen, C.A., Monroe, J.J., Hill, H.E., and Hooks, N.T., Jr.: Manual for alcoholic scales of the Inventory of Habits and Attitudes (IHA). *Psychological Reports* 25:947–973 (1969).

Scales designed to show individual differences in alcoholics and differences between alcoholics and other groups were developed by factor analytic and empirical methods using personality, demographic, and alcohol experience items from the Inventory of Habits and Attitudes (IHA). IHA was constructed by Monroe and Hill as a matched form of their Personal Inventory (PI). PI was designed to measure characteristics of opiate addicts, especially Acceptability for Psychotherapy (AP). Several studies have indicated the utility of AP. A Language of Addiction and General Alcoholic Scale differentiated alcoholics from opiate addicts, mentally ill, and normal Ss by 3 SD's. The factor structure of scales was similar in both alcoholics and nonalcoholics.

413. Jasinski, D.R. and Isbell, H.: A comparison of LSD–25 with (−)-Δ^9-*trans*-tetrahydrocannabinol (THC) and attempted cross tolerance between LSD and THC. *Psychopharmacologia* 14:115–123 (1969).

The objective and subjective effects of 0.5 and 1.5 μg/kg of LSD intramuscularly were compared with those of 75 and 225 μg/kg of (−)-Δ^9-*trans*-tetrahydrocannabinol by smoking in the same eight subjects. The objective effects of LSD and THC differed markedly. LSD increased body temperature, systolic and diastolic blood pressure, lowered the threshold for the knee jerk, and dilated the pupils. THC had none of these effects but caused more marked tachycardia than did LSD. The subjective effects of the two drugs could not be readily distinguished by the methods used. Both LSD and THC are psychotomimetic drugs. Patients tolerant to LSD were not cross-tolerant to THC, indicating that the mental effects of the two drugs are probably mediated by different mechanisms.

414. Jasinski, D.R., Martin, W.R., and Hoeldtke, R.: Progress report on the abuse potential of weak narcotic antagonists. *Committee on Problems of Drug Dependence.* Washington, D.C.: National Academy of Sciences, National Research Council, 1969.

Additional studies to assess the abuse potential of GPA–1657, profadol hydrochloride and propiram fumarate have continued. The basis of the present studies concluded that GPA–1657 is a typical morphinelike agent since it will not support morphinelike dependence, but studies indicate that pentazocine has an abuse potential which is greater

than that of nalorphine but less than that of codeine and propoxyphene. Profadol and propiram, on the other hand, are probably partial agonists of morphine which are capable of producing a high degree of euphoria and morphinelike physical dependence with drug-seeking behavior and will substitute for morphine in subjects dependent upon 60 mg of morphine per day. Profadol has probably a greater abuse potential than either codeine or *d*-propoxyphene. Propiram would also be judged to have a significant abuse potential with the ability to produce dependence which is probably less than that of codeine or *d*-propoxyphene.

415. Jones, B.E., Martin, W.R., and Jasinski, D.R.: Skin conductance responses to hypercapnia in man during a cycle of addiction to morphine. *Psychopharmacologia* 14:394–403 (1969).

Skin conductance changes during periods of stress induced by hypercapnia were studied during a cycle of addiction to morphine. Conductance changes were found to be dose dependent in both tolerant and nontolerant states. The effects of morphine on skin conductance changes induced by hypercapnia were similar to those effects previously observed on changes induced by electric shock.

416. Kay, D.C., Eisenstein, R.B., and Jasinski, D.R.: Morphine effects on human REM state, waking state and NREM sleep. *Psychopharmacologia* 14:404–416 (1969).

After 4 adaptation nights, IM doses of morphine sulfate (7.5, 15, 30 mg/70 kg) and placebo were studied in eight male postaddicts, using a crossover design with randomized block analysis to demonstrate significant drug effect. Morphine decreased the number and duration of REM periods, delayed the onset of the first REM period, and possibly increased the time between REM period onsets. Thus, morphine significantly decreased REM state (REMS), but did not alter the pattern of maximum REMS in late night. Morphine significantly increased waking state (WS) but did not alter the pattern of maximum WS in early night. Morphine significantly increased tension, and shifted maximum tension from early night to middle night. Morphine altered EEG sleep patterns; although NREM definitions were thus less certain, morphine appeared to increase NREM light sleep (stages 1 and 2) and decrease NREM deep sleep (stages 3 and 4). After an initial decrease in REMS by 30 mg/70 kg of morphine, an increase in REMS was noted in the third night of the two pilot study subjects. The arousal response to morphine seen in postaddicts needs further study in other populations and during the course of chronic morphine use.

417. Martin, W.R.: Protracted morphine abstinence in the rat and in man. *Umschau in Wissenschaft und Technik* 17:556–557, 1969.

418. Martin, W.R. and Jasinski, D.R.: Physiological parameters of morphine dependence in man—tolerance, early abstinence, protracted abstinence. *Journal of Psychiatric Research* 7:9–17 (1969).

The effects of chronic morphine intoxication and withdrawal on a variety of physiological variables were studied in seven subjects. During chronic intoxication, pupils were constricted and respiration was depressed, whereas, blood pressure, pulse rate, and body temperature were elevated. The abstinence syndrome that emerged following withdrawal had two phases. The early or primary phase was characterized by an increase in blood pressure, pulse rate, body temperature, respiratory rate, and pupillary diameter, and these signs lasted for 4–10 weeks. The protracted or secondary phase first began to emerge between the 6th and 9th weeks after complete withdrawal and persisted through the 26th week to 30th week. It was characterized by decreased blood pressure, pulse rate, body temperature, and pupillary diameter. A relationship between the protracted abstinence syndrome and relapse has been postulated and discussed.

419. Mulé, S.J.: Inhibition of phospholipid-facilitated calcium transport by central nervous system-acting drugs. *Biochemical Pharmacology* 18:339–346 (1969).

Narcotic analgesics effectively inhibit the binding of Ca^{2+} to phospholipids in vitro. Morphine and nalorphine also inhibit the Ca^{2+} transported by phospholipids obtained from guinea pig brain subcellular fractions. The inhibition of Ca^{2+} transported was related to ionization of the drug and was compared with the analgesic potency of the narcotic drugs. About 69 percent of morphine-^{14}C was bound to phosphatidic acid and this binding was inhibited by divalent ions (3–29 percent). Various CNS-acting drugs were also effective in inhibiting the transport of Ca^{2+} ions by phosphatidic acid. It is postulated that an alteration in the binding of ions to phospholipids within the neuronal membrane may be involved in the pharmacological actions of CNS-acting drugs.

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420. Eddy, N.B. and Martin, W.R.: Drug dependence of specific opiate antagonist type. *Pharmakopsychiatrie Neuro-Psychopharmakologie* 3:73–82 (1970).

The dependence producing liability of opiate antagonists nalorphine, cyclazocine, naloxone, pentazocine is described. Smaller doses of cyclazocine are commonly identified as an opiate, larger doses are identified as a barbiturate or amphetamine. Patients receiving opiate an-

tagonists chronically develop an abstinence syndrome qualitatively different to the morphine abstinence syndrome. Tolerance and dependence to the specific antagonists are induced by the agonistic component of opiate antagonists.

421. Essig, C.F.: Reduction of barbiturate dependence induced by repeated electroconvulsions. *Archives Internationales de Pharmacodynamie et de Therapie* 188:387–391 (1970).

Repeated electroconvulsions were administered to rats that had been drinking sodium barbital. This was done to decrease or prevent the occurrence of barbiturate abstinence convulsions when the drug was discontinued. The administration of electroconvulsions was associated with a significant reduction in the oral consumption of sodium barbital. Although physical dependence had probably developed the rats underwent a gradual withdrawal of the drug.

422. Gorodetzky, C.W.: Marihuana, LSD, and amphetamines. Drug Dependence 5:18–23 (1970).

In a brief review the pharmacology and toxicology of marihuana, LSD, and amphetamines is discussed as they relate to the abuse of these substances. For each compound the origin, pharmacologic effects, toxicologic effects, and characteristics of abuse are summarized.

423. Gorodetzky, C.W. and Christian, S.T.: *What You Should Know About Drugs.* New York: Harcourt-Brace-Jovanovich, Inc., 1970.

424. Haertzen, C.A.: Subjective effects of narcotic antagonists cyclazocine and nalorphine on the Addiction Research Center Inventory (ARCI). *Psychopharmacologia* 18:366–377 (1970).

The subjective effects of two doses of cyclazocine (0.6 mg and 1.2 mg/70 kg), nalorphine (16 and 32 mg/70 kg), no-drug and placebo were compared with 32 opiate addicts using drug sensitive scales of the Addiction Research Center Inventory (ARCI) items. The effects of these narcotic antagonists were highly similar on ARCI scales and items. Both drugs produced a general drug effect, difficulty in focusing eyes, physical weakness, tiredness, poor motivation, moodiness, misery, anxiety, tension, hallucinations, changes in sensation and perception, and inefficiency of physical, cognitive, and social functions. Cyclazocine was 15–26 times more potent than nalorphine. The effects of cyclazocine and nalorphine were differentiated from the effects of other drugs such as morphine, pentobarbital, and LSD when the overall pattern of effect was considered.

425. Haertzen, C.A., Meketon, M.J., and Hooks, N.T., Jr.: Subjec-

tive experiences produced by the withdrawal of opiates. *British Journal of Addiction* 65:245–255 (1970).

Past studies have suggested that the intensity of opiate withdrawal symptoms among opiate addicts volunteering for treatment is weak. To obtain a better measure of weak opiate withdrawal using the Addiction Research Center Inventory, the responses of 50 opiate addicts undergoing withdrawal treatment on day 2 after admission at the Clinical Research Center, Lexington, Ky., were compared with another 50 subjects tested 1 month after admission. The 84-item weak opiate withdrawal scale derived through this comparison was more effective for showing weak opiate withdrawal than prior withdrawal scales. Physical illness, tension, worry, dysphoria, insomnia, poor cognitive and social efficiency, loss of sense of humor, and a feeling of subjective need for the drug of choice characterize some of the common symptoms for weak and strong withdrawal. Symptoms such as goose pimples, hot and cold spells, sweating, watering eyes, difficulty in movement, cramps, and yawning are more common during strong opiate withdrawal.

426. Haertzen, C.A., Monroe, J.J., Hooks, N.T., Jr., and Hill, H.E.: The language of addiction. *The International Journal of the Addictions* 5:115–129 (1970).

The Personal Inventory (PI), designed for opiate addicts, and the Inventory of Habits and Attitudes (IHA), a matched form of the PI designed for alcoholics, were used to assess personality and drug-related experiences appropriate for, or specific to, the abuser's drug of choice. In experiment I, 61 men alcoholics were given the IHA and 61 opiate addicts matched in age, sex, race, and addiction status the PI. Significantly more drug-related items than personality items differentiated alcoholics from opiate addicts. In experiment II, another sample of 61 men opiate addicts were given the PI and still another 61 were given the IHA. More significant differences were obtained on the drug-related items than on personality items ($p<.01$). The effect of language (labeling) was more important when it was varied in the group of opiate addicts than when it was held constant in the comparison of opiate addicts and alcoholics in experiment I ($p<.01$). Scores of the opiate addicts on 40 items of the PI were higher than those on the corresponding IHA items. These 40 items formed the Language of Addiction (LAd) scale. In experiment III, the corresponding 40 items of the IHA were given to 271 men alcoholics, 81 opiate addicts, 24 physically ill, and 11 mentally ill men. Alcoholics scored significantly higher on the alcoholic LAd scale than nonalcoholics ($p<.001$), with practically no overlap in scores. Scores of the nonalcoholic groups were similar. When 271 alcoholics were given the alcoholic and 272 opiate addicts the opiate LAd scales, their scores did not differ, indicating that differences obtained

between groups depend largely on the appropriateness of the drug label used in the test items.

427. Hoeldtke, R.D. and Martin, W.R.: Urine volume and catecholamine excretion. *The Journal of Laboratory and Clinical Medicine* 75:166–174 (1970).

Large changes in urine volumes from human subjects were affected by systematically varying water intake. Twenty-four-hour catecholamine excretion was found to be unrelated to urine volume. The efficiency of the column chromatographic catecholamine extraction was lowered by both highly concentrated and highly dilute urine.

428. Hoeldtke, R.D. and Sloan, J.W.: Acid hydrolysis of urinary catecholamines. *The Journal of Laboratory and Clinical Medicine* 75:159–165 (1970).

Several recent modifications of the acid hydrolysis of urinary catecholamines have been studied with the method of Weil-Malherbe. The hydrolysis of the alumina filtrate as recommended by Fruehan and Lee is an effective way to measure directly the conjugate fraction. The pH of the hydrolysis and the ratio of alumina weight/urine volume are critical variables when this technique is used. Prehydrolysis dilution of urine, as recommended by Kahane and associates, led to a loss rather than a gain of catecholamine.

429. Jasinski, D.R. and Mansky, P.A.: The subjective effects of GPA–2087 and nalbuphine (EN–2234A). *Committee on Problems of Drug Dependence.* Washington, D.C.: National Academy of Sciences, National Research Council, 1970.

A single dose study comparing the subjective effects of nalbuphine, GPA–2087, morphine, and placebo indicated that GPA–2087 produced typical morphinelike subjective effects and euphoria. On the other hand, subjective effects of nalbuphine are not easily classified as being morphinelike or typically nalorphinelike but overall appear to more closely resemble the subjective effects produced by nalorphine and cyclazocine. Although there were some sedative effects, there were no significant responses on the LSD items even with a dose of 72 mg/70 kg which is 9 times the threshold dose for subjective effects and pupillary constriction. In addition, there was a plateauing on pupillary constriction at the 8-mg dose. Nalbuphine, but not GPA–2087, is a narcotic antagonist in man.

430. Jasinski, D.R., Martin, W.R., and Hoeldtke, R.D.: Effects of short- and long-term administration of pentazocine in man. *Clinical Pharmacology and Therapeutics* 11:385–403 (1970).

Pentazocine produces morphinelike subjective effects. A dose of 60 mg per 70 kg produces subjective effects which more closely resemble those of nalorphine than those of morphine. Pentazocine will not suppress abstinence symptoms in subjects dependent on either 60 or 240 mg per day of morphine. Pentazocine is 1/50 as potent as nalorphine in precipitating abstinence symptoms in subjects dependent on 240 mg of morphine per day. Long-term administration of pentazocine produces dependence which has elements of both morphine and nalorphine dependence. It is concluded that pentazocine has an abuse potential which is less than that with morphine but greater than that with nalorphine.

431. Jones, B.E., Essig, C.F., and Creager, W.: Intraventricular infusion of ethanol in dogs. Effect on voluntary alcohol intake. *Quarterly Journal of Studies on Alcohol* 31:288–292 (1970).

In six dogs cannulas were implanted in the left lateral cerebral ventricle. In five of these, slow infusion (6 ml per 24 hours) of several solutions of ethanol (10 to 25 percent v/v) were made over varying time periods (4 to 13 weeks). During the entire period, the intake of water and 10 percent ethanol, which were available ad libitum, was measured daily. No changes in water or ethanol consumption occurred in response to the intraventricular infusion of ethanol.

432. Krivoy, W.A.: Effects of ACTH and related polypeptides on spinal cord. *Progress in Brain Research* 32:107–119 (1970).

ACTH and related polypeptides are capable of altering transmission in the spinal cord under a variety of conditions. Although their action at this site supports the idea that they are active in synaptic transmission, and that they are able to modulate activity at this site, considerably more evidence is required before their importance or role can be ascertained.

433. Martin, W.R.: Commentary on the Second National Conference on Methadone Treatment. *The International Journal of the Addictions* 5:545–552 (1970).

The issues involved in the rigorous assessment of the efficacy of methadone maintenance in the treatment of narcotic addiction are discussed.

434. Martin, W.R.: Pharmacological redundancy as an adaptive mechanism in the central nervous system. *Federation Proceedings* 29:13–18 (1970).

Three types of evidence have been presented that are consistent with the concept that pharmacological redundancy may exist in the

central nervous system and that it may be a mechanism in the production of certain types of drug tolerance and dependence. The depression of certain functional pathways produced by large doses of neurohumoral antagonists can be surmounted by increasing stimulus strength. Since the quantity of neurohumoral transmitter that can be liberated by the presynaptic element is limited and would not be expected to surmount the depression produced by large doses of the antagonist, a neuronal shunt around the depressed synapse has been postulated. The redundancy theory requires that continuing activity of the drug is necessary for the hypertrophy of the redundant pathway and the development of tolerance and physical dependence. Several lines of evidence have been presented which indicate that the degree of morphinelike dependence is related to the strength of agonist activity and that the pharmacological activity of morphine persists in the tolerant animal. Finally, four distinct pharmacological mechanisms (cholinergic, adrenergic, tryptaminergic, and 5-hydroxy-tryptophanlike) have been identified which facilitate the flexor reflex and evoke the stepping reflex, both of which are signs of morphine dependence and abstinence. Although none of these mechanisms is probably essential, or even necessary, for the development of morphine dependence, their existence is consistent with the hypothesis that there is pharmacological redundancy in the spinal cord. There are two consequences of pharmacological redundancy that may be of importance to the issues of tolerance and dependence. One is related to the relative importance of the redundant pathway to the working of the functional system. When the affected redundant pathway occupies a subservient role, the effects of the agent may be superficially quite small and difficult to detect, especially if liminal stimuli are used. The other consequence is related to the capacity of the redundant pathway to hypertrophy. When its capacity to hypertrophy is limited, only partial tolerance can develop. To give a specific example, when one pathway is almost maximally depressed and the redundant pathway has only a limited ability to hypertrophy and can only partly assume the function, the system will be highly refractory to additional large doses of depressants (tolerance); nevertheless, a persisting depression will be seen (partial tolerance). As has been pointed out previously, this is the situation with regard to the respiratory depressant effect of morphine in the tolerant subject. On the other hand, if the redundant pathway has a large capacity to hypertrophy, then tolerance will be more complete, and upon withdrawal the large capacity of the redundant pathway will add to that of the affected pathway, giving rise to increased levels of excitation at the common pathway (which would be a sign of abstinence). Thus, the redundancy model would predict that a disease of adaptation, physical dependence, would occur only in those functional systems where the redundant pathway hypertrophies.

435. Martin, W.R. and Eades, C.G.: The action of tryptamine on the dog spinal cord and its relationship to the agonistic actions of LSD-like psychotogens. *Psychopharmacologia* 17:242–257 (1970).

In chronic spinal dogs, LSD, mescaline, psilocin, 2,5-dimethoxy-4-methylamphetamine, methysergide, and tryptamine facilitate the flexor reflex evoked by tetanic electrical stimulation of the toe and induce the stepping reflex. These effects are antagonized by chlorpromazine and cyproheptadine, but not by phenoxybenzamine. 5-Hydroxytryptophan and serotonin also facilitate the flexor reflex and evoke the stepping reflex, but these effects are not antagonized by cyproheptadine. These findings suggest that the mode of action of several LSD-like psychotogens is similar to that of tryptamine and is different from that of serotonin or 5-hydroxytryptophan.

436. Martin, W.R. and Sloan, J.W.: Effects of infused tryptamine in man. *Psychopharmacologia* 18:231–237 (1970).

Tryptamine, infused intravenously in man, facilitates the patellar reflex, dilates pupils and elevates blood pressure. It also causes changes in vision and hearing, as well as nausea, dizziness, sweating, and heaviness of body. These changes are similar to those produced by LSD-like hallucinogens and are consistent with the hypothesis that LSD-like hallucinogens interact with tryptamine receptors as one mode of action.

437. Martin, W.R., Sloan, J.W., and Eades, C.G.: The mode of action of LSD and its relationship to tryptamine: Studies in the chronic spinal dog and in man. *Committee on Problems of Drug Dependence.* Washington, D.C.: National Academy of Sciences, National Research Council, 1970.

438. Mulé, S.J.: Morphine and the incorporation of orthophosphate in vivo into phospholipids of the guinea pig cerebral cortex, liver and subcellular fractions. *Biochemical Pharmacology* 19:581–593 (1970).

This investigation was initiated to ascertain whether morphine in vivo would alter the incorporation of ^{32}orthophosphate into phospholipids of guinea pig cerebral cortex, liver, and subcellular organelles of these tissues. Morphine stimulated the incorporation of ^{32}orthophosphate into whole cerebral cortex phospholipids 119 percent at 16 h and 87 percent at 24 h after ^{32}orthophosphate as determined by total radioactivity measurements. A significant stimulation of the incorporation of ^{32}orthophosphate ranging from 41 to 207 percent occurred at 16 and 24 h with individual phospholipids. No statistically significant effect was observed with total radioactivity data obtained from whole liver, although significance was observed with phosphatidylinositol and phosphatidic acid at later time intervals. A predominantly stimulatory effect

on phospholipid metabolism was obtained with total radioactivity determinations on the subcellular fractions of the cerebral cortex. The major stimulatory effect occurred with the individual phospholipids at 48 h in the soluble supernatant fraction (248–403 percent). Total radioactivity studies with liver subcellular fractions provided a statistically significant effect at 48 h (79–134 percent). The effect on individual phospholipids from liver subcellular fractions was similar to the total radioactivity data. Morphine had both an inhibitory and stimulatory effect on the total radioactivity determinations of mitochondrial subfractions from the cerebral cortex at 16, 24, and 48 h. A similar effect was observed with mitochondrial fractions subjected to osmotic shock. Total radioactivity determinations on phospholipids from microsomal subcellular fractions of liver were both stimulatory and inhibitory at the various time intervals. A statistically significant stimulatory effect was observed with individual phospholipids at 48 h from the smooth and rough microsomal liver subcellular fractions. It is concluded that morphine alters phospholipid metabolism in vivo and thus may directly affect cellular function in liver and neuronal activity in the central nervous system.

439. Wikler, A. and Essig, C.F.: Withdrawal seizures following chronic intoxication with barbiturates and other sedative drugs. In: Niedermeyer, W. (ed.): Vol. 4, *Epilepsy, Modern Problems in Pharmacopsychiatry,* pp. 170–184. Basel, Switzerland: S. Karger, 1970.

Clinical aspects of barbiturate intoxication and withdrawal are described, together with the EEG characteristics of both states. Emphasis is placed on the seizure aspects of such withdrawal and the increased susceptibility of such patients to photostimulation (as described by Wulff) is also noted. Basic work related to the underlying mechanisms of the barbiturate abstinence seizures is reviewed briefly. The nonbarbiturate sedative or hypnotic drugs that have been associated with barbituratelike states of intoxication and withdrawal are listed. Alcohol withdrawal convulsions in both man and animal are discussed in the context of EEG changes as well as "metabolic" and "tissue" tolerance. The myoclonic, convulsive and/or paroxysmal EEG responses to photostimulation that peak between the 33d and 45th hours of alcohol withdrawal are also noted. The treatment of barbiturate and nonbarbiturate sedative withdrawal is discussed. The substitution and gradual dosage reduction of pentobarbital is recommended as safe treatment. The use of diphenylhydantoin (Dilantin) and/or phenothiazines as a substitute for or as an adjunct to the treatment of sedative abstinence convulsions is not recommended. After the pharmacotherapy of the withdrawal syndrome is completed it is advised that a psychiatric exploration of underlying emotional and adjustment problems be carried out.

1971

440. Christian, S.T., Gorodetzky, C.W., and Lewis, D.V.: Structure-activity relationships of normeperidine congeners on cholinesterase systems in vitro and analgesia in vivo. *Biochemical Pharmacology* 20:1167–1182 (1971).

The relative importance of hydrophobic or Van der Waals forces has been evaluated in a quantitative manner with regard to the binding of a series of N-alkyl substituted normeperidine homologs to both acetyl- and butyrylcholinesterases. The normeperidine compounds gave mixed inhibition with both enzymes when acetylcholine was used as substrate. However, the mixed inhibition changed to pure noncompetitive with acetylcholinesterase when the hexyl through the decyl substituted normeperidines were used. Both the competitive (K_I) and noncompetitive (K_I') inhibitor dissociation constants were determined for the enzyme systems. With butyrylcholinesterase, simple linear relationships were observed when alkyl chain length, R_m values, and molecular parachors were plotted as a function of the logarithm of the inhibitor dissociation constants. Linear relationships were not observed, however, with acetylcholinesterase. The suggestion is put forth that many of the differences between the two enzyme systems may be explained on the basis of a difference in the physical characteristics of the nonpolar region in the vicinity of their active sites. Binding energies were determined with the inhibitor series for both systems and carbon-carbon distances were calculated between enzyme and inhibitor molecules from these data. The analgesic potencies of the normeperidine congeners were determined by the hot-plate method and, when plotted as a function of alkyl chain length, showed similarities to the acetylcholinesterase kinetic data and to other physical-chemical parameters. These observations may indicate similarities in the nature of the acetylcholinesterase active center and the analgesic receptor. Calculations also indicated that a change in binding energy of only 0·3 kcal/mole is reflected as a change in the ED_{50} of 50 percent in going from the butyl to the pentyl normeperidine derivatives.

441. Christian, S.T. and Janetzko, R.: A comparative study of the interactions of the nonpolar fluorescent ligand, 1-anilino-8-naphthalene sulfonic acid, with butyryl and acetylcholinesterase. *Archives of Biochemistry and Biophysics* 145:169–178 (1971).

The binding of 1-anilino-8-naphthalene sulfonic acid (ANS) to both horse serum butyrylcholinesterase and eel acetylcholinesterase is accompanied by a marked increase in the fluorescence quantum yield of the dye and is associated with a 30-nm shift in the fluorescent emission of

the fluorochrome toward the blue region of the spectrum. Acetylcholinesterase appears to have three binding sites for the dye while butyrylcholinesterase has two. ANS inhibits the catalytic activity of both enzymes in an "uncompetitive" manner. The interaction of the dye with acetylcholinesterase brings about an irreversible inactivation of the enzyme. Binding constants, classical kinetic constants, and kinetic constants relating to inactivation have been calculated.

442. Gorodetzky, C.W.: Sensitivity of thin-layer chromatography for detection of opioids, cocaine and quinine. *Committee on Problems of Drug Dependence.* Washington, D.C.: National Academy of Sciences, National Research Council, 1971.

A method has been presented to estimate the sensitivity of thin-layer chromatography in terms of the amount which can be identified (termed the "IA") a given percentage of the time. From sensitivity data for the detection of 16 opioids, cocaine and quinine it is concluded:

1. Thin-layer chromatography is not uniformly sensitive for the detection of all opioids: and,
2. Following iodoplatinate stain with ammoniacal silver nitrate and potassium permanganate usually increases sensitivity for the detection of opioids.

From Rf data it is concluded that the Rf measurement of a single unknown spot is a poor measure of specificity.

443. Haertzen, C.A. and Hooks, N.T., Jr.: Contrast effects from simulation of subjective experiences: a possible standard for behavioral modification. *British Journal of the Addictions.* 66:225–227 (1971).

It was possible to improve the self-concepts of male opiate addicts for their no-drug state by using a technique designed to produce contrast effects that was suggested by Helson's Adaptation Level theory. Opiate addicts (N=35) regarded themselves as more efficient, healthy, and pleasant under a no-drug state when they were first asked to remember how they felt when they were sick, as with the flu or during opiate withdrawal. Another group (N=27) remembered more negative symptoms for sickness conditions when they were first asked to simulate experiences for a no-drug state.

444. Hill, H.E., Jones, B.E., and Bell, E.C.: State dependent control of discrimination by morphine and pentobarbital. *Psychopharmacologia* 22:305–313 (1971).

Rats were trained in state dependent discrimination to escape shock in a T-maze by turning one way under a drug and the other way under saline without aid of exteroceptive cues. In experiment 1, 9.0 mg/kg of

morphine, 20 mg/kg of pentobarbital and 0.3 cm^3 of saline were used with a balanced order of training which employed 18 training days under one condition followed by 18 days in the other condition; 12 test days were then given in which conditions were alternated daily. Pentobarbital produced strong state dependent behavior but morphine did not. Experiment 2 used 4.5, 9.0, 18.0, and 36.0 mg/kg of morphine and 0.3 cm^3 of saline with the same procedures as for the first study. Orderly state dependent learning was not found. In experiment 3, the dose levels and procedures were the same as for the second study except that training under the two conditions was carried out concurrently, i.e., morphine and saline trials were given alternately in balanced order. Highly significant dose-related state dependent behavior occurred in both the training and test periods. The results were discussed in relation to state dependent learning, dissociation, and opiate addiction.

445. Jasinski, D.R., Haertzen, C.A., and Isbell, H.: Review of the effects in man of marijuana and tetrahydrocannabinols on subjective state and physiologic functioning. *Annals of the New York Academy of Sciences* 191:196–205 (1971).

Studies in man at the Addiction Research Center with Δ^9-tetrahydrocannabinol (THC), pyrahexyl and the dimethylheptyl derivative of *dl*-synthetic THC (DMHP) indicate that Δ^9-THC is an hallucinogen whose activity is related to dose. In sufficient amounts Δ^9-THC will produce a toxic psychosis. Δ^9-THC, pyrahexyl and DMHP produce a common set of subjective effects and physiologic changes and may differ only in such characteristics as potency, onset, and duration of action. The present scales measuring subjective responses of tetrahydrocannabinols, for the most part, reflect the hallucinogenic activity of these drugs, which is distinct from that produced by LSD. Many of the symptoms are common to other psychoactive agents including the ability to produce euphoria. Tolerance develops with chronic pyrahexyl and marihuana administration in man. Abrupt withdrawal of the chronic administration of pyrahexyl and possibly marihuana produces a syndrome possibly indicative of physical dependence; however, the specific psychological, behavioral, and physiological changes in relation to drug-seeking behavior have not yet been documented.

446. Jasinski, D.R., Martin, W.R., and Hoeldtke, R.D.: Studies of the dependence-producing properties of GPA–1657, profadol, and propiram in man. *Clinical Pharmacology and Therapeutics* 12:613–649 (1971).

GPA–1657, profadol, and propiram are proposed as analgesics of low-abuse potential since none will suppress but each will precipitate abstinence in morphine-dependent monkeys. GPA–1657 is not an an-

tagonist in man but a typical morphinelike compound and is judged to have significant abuse potential. Profadol and propiram act as antagonists in man and precipitate abstinence in subjects dependent on 240 mg of morphine per day. As agonists, profadol and propiram resemble morphinelike rather than nalorphinelike drugs, since both produce morphinelike subjective effects and physical dependence and suppress abstinence in subjects dependent on 60 mg per day of morphine. Both were judged to have abuse potential. Propiram was judged to have somewhat less abuse potential than profadol, since it produces less euphoria and less physical dependence. The morphine antagonist properties of profadol and propiram are thought to be caused by the fact that they are morphine agonists with less intrinsic activity than morphine.

447. Jasinski, D.R., Martin, W.R., and Mansky, P.A.: Progress report on the assessment of the antagonists nalbuphine and GPA–2087 for abuse potential and studies of effects of dextromethorphan in man. *Committee on Problems of Drug Dependence.* Washington, D.C.: National Academy of Sciences, National Research Council, 1971.

GPA–2087 suppresses morphine abstinence in man. On the basis of both single dose and substitution studies, GPA–2087 is a morphinelike agent in man. Nalbuphine will precipitate abstinence in subjects dependent upon 60 mg of morphine per day, being one-fourth as potent as nalorphine. Direct addiction studies with nalbuphine indicate that nalbuphine will produce physical dependence and cannot be classified clearly, with characteristics that resemble both those of morphine and nalorphine. Most importantly, the withdrawal syndrome was uncomfortable and subjects exhibited drug-seeking behavior such that nalbuphine cannot be classified as a nalorphinelike agonist. Overall, the abuse potential of nalbuphine was felt to be similar to that produced by pentazocine. Subcutaneously or orally administered dextromethorphan produced subjective and physiologic effects which were distinct from those of morphine; on the other hand, some of the effects of dextromethorphan resemble those produced by nalorphine. In contrast to nalorphine which constricted pupils, dextromethorphan produced dose-related increases in pupil size.

448. Martin, W.R.: Drug dependence. In: DiPalma, J.R. (ed.): *Drill's Pharmacology in Medicine*, pp. 362–378. New York: McGraw-Hill, 1971.

449. Martin, W.R.: The use of the narcotic antagonists in the treatment of heroin dependence. *New York Law Journal* 166:34 (1971).

The role of the pathophysiology and psychopathology of narcotic addiction in relapse are discussed, as well as the possible role of cyclazocine in the treatment of narcotic addiction.

450. Martin, W.R., Jasinski, D.R., and Mansky, P.A.: Characteristics of the blocking effects of EN–1639A (N-cyclopropylmethyl-7,8-dihydro-14-hydroxy-normorphinone). *Committee on Problems of Drug Dependence.* Washington, D.C.: National Academy of Sciences, National Research Council, 1971.

It would thus appear that EN–1639A is twice as potent as naloxone and cyclazocine as an antagonist. Its duration of action is longer than that of naloxone; however, it is shorter than that of cyclazocine. It probably has agonistic activity of the nalorphine type, namely, it elevates blood pressure, constricts pupils, and produces racing thoughts and irritability, as well as other psychotomimetic effects; however, in this regard its activity is much less than that of cyclazocine. The efficacy of EN–1639A by the oral route is considerably greater than that of naloxone but less than that of cyclazocine. To produce a degree of antagonism that would be equivalent to that of 4–8 mg of cyclazocine daily, a daily dose of 50 to 100 mg of EN–1639A will probably have to be administered. The feasibility of administering this dose will have to be investigated; however, because of the great potency of EN–1639A, it is entirely conceivable that this agent could be administered in a depot which could provide blockade for a week or more.

451. Martin, W.R., Jasinski, D.R., and Mansky, P.A.: A comparison between subcutaneously administered morphine and subcutaneously and orally administered methadone on pupils and subjective effects. In: *Proceedings Third National Conference on Methadone Treatment,* PHS Publication 2172, pp. 53–54. Washington, D.C.: Government Printing Office, 1971.

Subcutaneously administered methadone was found to produce subjective changes and pupillary constriction and in these regards was equipotent to morphine. Orally administered methadone was about half as potent as subcutaneously administered morphine. The duration of action of methadone using subjective effects was approximately equal to that of morphine; however, its effects on pupils had a much longer duration of action.

452. Martin, W.R., Sloan, J.W., Sapira, J.D., and Jasinski, D.R.: Physiologic, subjective, and behavioral effects of amphetamine, methamphetamine, ephedrine, phenmetrazine, and methylphenidate in man. *Clinical Pharmacology and Therapeutics* 12:245–258 (1971).

Five centrally acting sympathomimetic amines, *d*-amphetamine, *d*-methamphetamine, ephedrine, phenmetrazine, and methylphenidate, were studied in man. All of these agents increased blood pressure and respiratory rate, produced similar types of subjective changes, and increased the excretion of epinephrine. With regard to these parameters, there was a high concordance between estimates of their relative potencies. The concordance between the potency estimates for the different parameters suggests, but does not prove, that these five agents share a common mode of central action. Further, if the peripheral modes of action as elucidated by animal studies are true for man, this study suggests that it is unlikely that their central actions in man are a consequence of the release of norepinephrine in the brain.

453. Sloan, J.W.: Corticosteroid hormones. In: D.H. Clouet (ed.): *Narcotic Drugs: Biochemical Pharmacology*, pp. 262–282 New York: Plenum Press, 1971.

Single doses of morphine and other narcotic analgesics are either without effect or decrease 17–OHCS excretion in man and the guinea pig; whereas, the adrenal cortical response in the unanesthetized rat, dog, and mouse is increased, an effect which is probably antagonized by nalorphine. The urinary excretion of 17–KS is depressed in both man and the rat following single doses of morphine. The chronic administration of morphine suppresses steroid excretion in man and the rat although the adrenal gland of the rat is hypertrophied. Chronically administered nalorphine antagonizes this effect on steroids in the rat. Some tolerance develops to these depressant effects of morphine in both species. During early abstinence both man and the rat show signs of adrenal cortical stimulation which subside during protracted abstinence. In man, morphine dependence does not impair the ability of the adrenal gland to respond to exogenously administered ACTH; whereas, in the rat it may produce a dose related depression of the adrenal cortical response to ACTH and in vitro experiments suggest that there may be some alteration in steroid biosynthesis and biotransformation. Single doses of morphine antagonize the adrenal cortical response to cold exposure and carbon tetrachloride. Pentobarbital antagonized the effect of morphine on the adrenal cortical response and morphine in turn blocks the adrenal cortical stimulating effect of a variety of diverse stimuli in the pentobarbital-anesthetized rat but does not inhibit the response to hypothalamic and neurohypophyseal extracts. Further, neither hypophysectomy nor pentobarbital-morphine treatment blocks the effect of ACTH in the rat. These experiments suggest that morphine's site(s) of action is central to the adrenal gland and the pituitary and that the adrenal cortical effects are probably mediated through the simulation and inhibition of the release of CRF(s).

1972

454. Christian, S.T.: Enzymes. In: Mulé, S.J. and Brill, H. (eds.): *Chemical and Biological Aspects of Drug Dependence*, pp. 449–463. Cleveland, Ohio: Chemical Rubber Co. Press, 1972.

455. Gorodetzky, C.W.: Sensitivity of thin-layer chromatography for detection of 16 opioids, cocaine and quinine. *Toxicology and Applied Pharmacology* 23:511–518 (1972).

A method has been developed to evaluate quantitatively the sensitivity of thin-layer chromatography (TLC). For each drug studied, seven different amounts of the drug and a solvent control are randomly spotted across a 20×20 cm thin-layer plate. Ten to 30 such plates are made with the technician blind to the order of spotting. For each amount of drug, the ratio of (number of spots detected)/(number of spots plated) is determined, converted to percentage and plotted on log probability paper. The method of Litchfield and Wilcoxon is used to determine the amount which can be identified any given percentage of the time (termed the "identifiable amount" or IA) and its 95 percent confidence limits. Sensitivity data for 16 opioids, cocaine, and quinine, using iodoplatinate alone and followed by ammoniacal $AgNO_3$ and $KMnO_4$ for spot detection, show that TLC is not uniformly sensitive for the detection of all opioids. Adding $AgNO_3$ and $KMnO_4$ after iodoplatinate produced an increase in sensitivity, with the exception of the arylpiperidines studied, levallorphan, propoxyphene, cocaine, and quinine. A relative detection index for each drug, taking into account sensitivity for detection by TLC, euphorogenic dose and 24 h urinary excretion relative to morphine showed that all opioids would not be predicted to be equally detectable in the urine following administration of equieuphorogenic doses. R_f data show widely overlapping tolerance limits between drugs, indicating that the R_f of a single unknown spot would be expected to be a poor measure of specificity under these TLC conditions.

456. Gorodetzky, C.W.: Urinalysis: Practical and theoretical considerations. *Proceedings of the Fourth National Conference on Methadone Treatment* pp. 155–156. New York: National Association for the Prevention of Addiction to Narcotics, 1972.

Three important parameters of urine screening methods are defined and discussed: specificity (ability of a method to distinguish among compounds); sensitivity (minimal detectable concentration of drug in the urine); validity (ability of a method to detect a drug or its metabolites in biological fluid following human drug use).

457. JASINSKI, D.R.: Effects in man of partial morphine agonists. In: Kosterlitz, H.W., Collier, H.O.J. and Villarreal, J.E. (eds): *Agonist and Antagonist Actions of Narcotic Analgesic Drugs; Proceedings of the Symposium of the British Pharmacological Society, Aberdeen, July 1971*, pp. 94–103. London: MacMillan Press, 1972.

Studies of the dependence liability of a number of morphine antagonists have revealed that certain of these compounds have morphinelike agonist properties. The analgesic drug, profadol, was concluded to be a partial agonist of the morphine type since it produces subjective effects and physical dependence which are morphinelike rather than nalorphinelike and will suppress abstinence in subjects dependent upon 60 mg of morphine per day; on the other hand, it will precipitate abstinence in subjects dependent upon 240 mg of morphine per day. Pentazocine was also thought to have partial agonist activity of the morphine type since it produces subjective effects and physical dependence that are both morphinelike and nalorphinelike; pentazocine, however, will not suppress abstinence in subjects dependent upon 60 mg of morphine per day. As a consequence, profadol was concluded to have a high abuse potential approaching that of morphine. Pentazocine, on the other hand, was concluded to have an abuse potential greater than nalorphine or cyclazocine, but an abuse potential less than compounds such as *d*-propoxyphene or codeine.

458. JASINSKI, D.R.: Studies on the subjective effects of narcotic antagonists. In: Keup, W. (ed.): *Drug Abuse: Current Concepts and Research*, pp. 270–276. Springfield, Ill.: Charles C Thomas, 1972.

The subjective effects produced by the narcotic antagonists, nalorphine, cyclazocine, naloxone, profadol, and pentazocine, are quite diverse. In low doses, nalorphine and cyclazocine produce opiatelike subjective effects and subjective feelings of well-being, relaxation, elation, and euphoria. With larger doses both cyclazocine and nalorphine produce apathetic sedation as well as psychotomimetic effects. Recent studies indicate that other narcotic antagonists produce subjective effects which differ markedly from those of nalorphine. In man, the narcotic antagonist naloxone does not produce any significant subjective or physiologic changes when administered acutely or chronically and is considered a pure antagonist. Profadol, on the other hand, produces typical morphinelike subjective effects and euphoria while pentazocine produces subjective effects which resemble both those of morphine and nalorphine. The pattern of subjective effects for each of these agents is consistent with the concepts of receptor dualism and competitive dualism.

459. JASINSKI, D.R. and MANSKY, P.A.: Evaluation of nalbuphine

for abuse potential. *Clinical Pharmacology and Therapeutics* 13:78–90 (1972).

Nalbuphine is a narcotic antagonist and analgesic. A dose of 8 mg per 70 kg of nalbuphine in man produces subjective effects which resemble those of 10 mg per 70 kg of morphine. Nalbuphine, in doses of 24 and 72 mg per 70 kg, produces mild effects which more closely resemble those of nalorphine. Nalbuphine is one-fourth as potent as nalorphine in precipitating abstinence in subjects dependent on 60 mg of morphine per day. Chronic administration of nalbuphine produces physical dependence which resembles that produced by pentazocine, since it has elements of both morphine and nalorphine dependence. It is concluded that nalbuphine has an abuse potential which approximates that of pentazocine, but equianalgesic doses of nalbuphine produce less nalorphinelike effects than does pentazocine.

460. Jasinski, D.R. and Nutt, J.G.: Progress report on the assessment program of the NIMH Addiction Research Center. *Committee on Problems of Drug Dependence.* Washington, D.C.: National Academy of Sciences, National Research Council, 1972.

Studies of mixtures of dextroamphetamine and morphine as well as dextroamphetamine alone indicate that amphetamine adds to the euphoria of morphine but does not significantly enhance the euphoria. Complex physiologic interactions between morphine and dextroamphetamine were observed but it appears that dextroamphetamine antagonizes the respiratory depression and miosis produced by morphine while morphine antagonizes the thermogenic effect of amphetamine. Single doses of intravenously administered methadone produced subjective effects and euphoria to a degree which was similar to those produced by single doses of morphine and heroin, with methadone being equally potent to morphine and heroin being about twice as potent. Administered orally and subcutaneously, methadone again produced typical morphinelike subjective effects and euphoria. Orally and subcutaneously administered methadone and morphine were equally potent but when administered orally methadone was only about one-half as potent. Evaluation of the abuse potential of methadone and naloxone mixtures indicates that when administered in single doses naloxone blocks the effects of methadone for 1 or 2 hours, after which typical morphinelike subjective effects and euphoria produced by methadone emerged. Overall, an additional study indicated that the administration of methadone once weekly produced physical dependence to a degree that the administration of naloxone was precipitating a mild abstinence syndrome. Simultaneous administration of methadone and naloxone to subjects physically dependent on morphine indicated that the methadone did attenuate the overall intensity of the

abstinence syndrome precipitated by naloxone. However, this was true only after the first 15 minutes and is attributed to the slower onset of action of methadone rather than the action of naloxone in precipitating abstinence. In subjects dependent upon 30 mg of morphine per day neither pentazocine nor nalbuphine precipitated abstinence in a 24-hour substitution test. Precipitation studies with naloxone and nalorphine indicate that nalorphine was approximately 1/25th as potent as naloxone in subjects dependent upon 30 mg of morphine per day, indicating that at low levels of morphine dependence larger doses of nalorphine are required to precipitate abstinence. Study of the duration of action of naloxone pamoate suspended in 2 percent aluminum monosterate in sesame oil indicate that this formulation will extend the blocking action of naloxone to about 24 hours in man but this degree of blockade is not complete and produces only slight modification in the effects of the 30 mg test dose of morphine. Additional observations of precipitated abstinence suggest that there must be a relatively rapid release of naloxone from the injection site.

461. Kay, D.C., Jasinski, D.R., Eisenstein, R.B., and Kelly, O.A.: Quantified human sleep after pentobarbital. *Clinical Pharmacology and Therapeutics* 13:221–231 (1972).

Intramuscular doses of pentobarbital (75, 150, 300 mg per 70 kg) and placebo were given to eight male postaddict subjects at weekly intervals. After 4 adaptation nights, a crossover design with randomized block analysis of variance was used to demonstrate significant ($p<0.05$) drug effect. Pentobarbital decreased rapid eye movement sleep (REMS) by decreasing the number and duration of REMS episodes and by delaying the onset of the first REMS episode, without measurably changing the period of the REMS cycle. Pentobarbital also decreased the prevalence of eye movements and of disruptions during REMS. Pentobarbital increased spindle (stage 2) sleep and spindle burst incidence during stage 2 sleep but had minimal effect on delta (stages 3 and 4) sleep. Pentobarbital decreased muscle tension and body movements but had little effect on EEG measures of waking state. The combined reduction of REMS and increase of spindle sleep might be used as a standard effect with which to determine equivalent doses of barbiturates and similar hypnotics.

462. Martin, W.R.: The assessment of the abuse potentiality of narcotic analgesics. In: Keup, W. (ed.): *Drug Abuse; Current Concepts and Research.* pp. 69–72. Springfield, Ill.: Charles C Thomas, 1972.

Methods of characterizing drugs qualitatively using subjective effects as measured by questionnaires and the abstinence syndrome using the methods of Himmelsbach are described.

463. MARTIN, W.R.: Pathophysiology of narcotic addiction: possible roles of protracted abstinence in relapse. In: Zarafonetis, C.J.D. (ed.): *Drug Abuse; Proceedings of the International Conference (Ann Arbor, Mich., Nov. 1970)*, pp. 153–159. Philadelphia: Lea & Febiger, 1972.

The characteristics of protracted abstinence in the rat and man are reviewed in this paper as well as the relationship of this phenomenon and relapse in the rat. The pathologic significance of protracted abstinence is discussed as well as conditioned abstinence and drug-seeking behavior.

464. MARTIN, W.R. and EADES, C.G.: Cross tolerance to tryptamine in the LSD tolerant dog. *Psychopharmacologia* 27:93–98 (1972).

Infusions of LSD or tryptamine increase heart rate, respiratory rate, and pupillary diameter, facilitate the flexor reflex and evoke the stepping reflex in the chronic spinal dog. When LSD is administered twice daily in a dose of 15 μg/kg subcutaneously, tolerance develops to these effects of LSD and cross-tolerance to these effects of tryptamine. These observations support the concept that tryptamine and LSD have a common mode of action and the hypothesis that LSD exerts some of its pharmacologic effects by acting as an agonist at tryptamine receptors.

465. MARTIN, W.R., GORODETZKY, C.W., and THOMPSON, W.O.: Receptor dualism: some kinetic implications. In: Kosterlitz, H.W., Collier, H.O.J., and Villarreal, J.E. (eds.): *Agonist and Antagonist Actions of Narcotic Analgesic Drugs: Proceedings of the Symposium of the British Pharmacological Society, Aberdeen, July 1971,* pp. 30–44. London: MacMillan Press, 1972.

One form of the equation for receptor dualism is presented; namely, when one agonist is a strong or partial agonist at the morphine receptor and another agonist is a competitive antagonist at the morphine receptor and a strong or partial agonist at the nalorphine receptor. Calculations were done on a PDP–12 computer and families of curves for different dissociation constants and intrinsic activities were graphed. Three families of curves could be identified. Interaction curves between nalorphine and the morphinelike agonists could be identified depending on the relative affinities at the two receptors and their intrinsic activities. These interaction curves showed a concavity downward, a concavity upward and a family of curves which were not biphasic. Whether the curve is concave downward or upward depends upon whether the nalorphinelike drug's affinity for the morphine receptor is greater or less than its affinity for the nalorphine receptor and whether it displaces morphine faster from the morphine receptor. The third case was when receptor dualism could not be differentiated from an interaction between a strong agonist and a partial agonist.

466. Martin, W.R. and Jasinski, D.R.: The mode of action and abuse potentiality of narcotic antagonists. In: Janzen, R., Keidel, W.D., Herz, A., and Steichele, C. (eds.) and Payne, J.P., and Burt, R.A.P. (eds., English edition): *Pain: Basic Principles—Pharmacology—Therapy*, pp. 225–234. Stuttgart: Georg Thieme Publishers, 1972.

The characteristics of morphine- and nalorphinelike drugs as well as their kinetic interactions are discussed in the development of the two-receptor theory. Further, the practical implications of the two-receptor theory and the identification of the abuse potentiality of both morphine- and nalorphinelike drugs are discussed. The use of subjective questionnaires as well as the ability of drugs to suppress morphinelike abstinence in the assessment of their abuse potentiality is described.

467. Martin, W.R. and Sandquist, V.L.: Long-acting narcotic antagonists. *Committee on Problems of Drug Dependence.* Washington, D.C.: National Academy of Sciences, National Research Council, 1972.

468. Martin, W.R., Sloan, J.W., Christian, S.T., and Clements, T.H.: Brain levels of tryptamine. *Psychopharmacologia* 24:331–346 (1972).

A modification of the method of Hess and Udenfriend for the extraction and identification of tryptamine, as well as a gas chromatographic method for identifying tryptamine, has been described. Tryptamine, using these methods, as well as thin-layer chromatography, has been identified in steer, dog, and human brain. Tryptamine was not found in the rat brain. In the dog, isocarboxazid increased brain and spinal cord tryptamine levels two or three times. In view of the fact that tryptamine resembles LSD-like hallucinogens in many of its actions, it is suggested that tryptamine may be a naturally occurring hallucinogen that may play a role both in normal and pathologic functioning of the brain.

1973

469. Cone, E.J.: Human metabolite of naltrexone (N-cyclopropylmethylnoroxymorphone) with a novel C–6 isomorphine configuration. *Tetrahedron Letters* 28:2607–2610 (1973).

The major urinary metabolite of naltrexone in man was isolated and identified as 6β-hydroxynaltrexone, a novel metabolite with an isomorphine configuration at C–6. The metabolite was isolated by TLC and crystalized as the hydrochloride. Both the IR and fluorescence

spectra of the metabolite indicated a similar but nonidentical structural relationship with the α-isomer, available as a standard. Final structural proof was achieved by an Oppenauer oxidation of the hydroxy-metabolite to the parent ketocompound. This is the first reported example of metabolic reduction of a morphine-related compound to a metabolite with the C–6 isomorphine configuration.

470. Gorodetzky, C.W.: Efficiency and sensitivity of two common screening methods for detecting morphine in urine. *Clinical Chemistry* 19:753–755 (1973).

Modified procedures are described for extracting morphine from urine with organic solvents and with paper impregnated with ion-exchange resin, followed by detection by thin-layer chromatography. I propose that efficiency of extraction (percent recovery) be defined in terms of the amount of drug reaching the detection system versus the amount in the total urine sample analyzed. Percent recoveries were determined experimentally with 95 percent confidence limits and 95 percent, P=.05 tolerance limits, and were 60.6 percent for the organic solvent procedure and 48.2 percent for the ion-exchange paper procedure. Sensitivity of the overall detection method can be defined as the concentration of drug in the urine detectable at least 99 percent of the time. Values (95 percent confidence limits) determined experimentally were 0.19 (0.14–0.25) μg/ml for the organic solvent procedure and 0.16 (0.07–0.35) μg/ml for the ion-exchange paper procedure.

471. Gorodetzky, C.W.: Validity of urine tests in monitoring drug abuse. *Committee on Problems of Drug Dependence.* Washington, D.C.: National Academy of Sciences, National Research Council, 1973.

The sensitivity, specificity, and validity of various urine screening methods are briefly discussed and summarized. In experimental validity studies, following single minimally to moderate euphorigenic doses of heroin there was a high probability of detection of morphine in the urine for only the first 8 hours following i.v. administration using TLC procedures without hydrolysis and the Technicon Autoanalyzer with sensitivities in the range of .1 to .25 μg/ml. With TLC and hydrolysis and the free radical assay technique there was a moderate probability of detection to 16 hours. With the radioimmunoassay there was a high probability of detection for 32–40 hours and moderate probability out to 48 hours. From this data it would be predicted that there would be a high probability of detecting a chronic heroin user, using as little as 2.5 to 5.0 mg three times per day, by the least sensitive TLC procedures without hydrolysis.

472. Haertzen, C.A. and Hooks, N.T., Jr.: Dictionary of drug associ-

ations, to heroin, benzedrine, alcohol, barbiturates and marijuana. *Journal of Clinical Psychology,* Monograph Suppl. No. 37, April 1973.

A 3,500-word dictionary of drug associations was constructed by having 20 or more opiate addicts associate words to heroin, benzedrine, alcohol, goofballs, and reefers. Broad sampling of words was attempted through selection of the 1,000 most frequently used English words (Thorndike and Lorge) and a word to represent each of 1,000 concepts in Roget's International Thesaurus. Sampling of the Osgood verbs of intention and semantic differential adjectives, meaningful and nonmeaningful nouns (Paivio, et al.), words used in various free association tests, adjectives used for measurement of subjective states (Nowlis, et al.), drug relevant words (23 categories), drug (Lingeman) and alcoholic slang (Rubington) was done to facilitate the analysis of the relationships between various linguistic categories and patterns of drug associations. It was thought that associations for a given drug would be accounted for by culturally determined verbal connections in all Ss and in part by the habit strength for a particular drug. The predominance of heroin associations in heroin addicts seems consistent with the notion that some portion of associations may be attributed to habit strength. Opiate addicts gave a large number of associations to reefers (marihuana), somewhat fewer associations for alcohol, and very few associations for goofballs (barbiturates), and benzedrine. The dictionary may be useful as a resource for the selection of words for studies of conditioning, verbal learning, perception, or individual differences, cues for possible educational objectives on drugs, evaluation of the drug relatedness of words chosen for experiments by some nondictionary criteria, and as a standard to compare the associational values of other drug users or addictive types with different presumed habit strengths.

473. Jasinski, D.R.: Assessment of the dependence liability of opiates and sedative-hypnotics. In: Goldberg, L. and Hoffmeister, F. (eds.): *Bayer-Symposium IV, Psychic Dependence,* pp. 160–170. Berlin-Heidelberg-New York: Springer-Verlag, 1973.

Assessment of analgesics is based upon the demonstration of morphinelike subjective effects and physical dependence as demonstrated in substitution tests or direct addiction tests. Similar relative potencies in comparison to morphine for scales measuring subjective effects, miosis, suppression of abstinence and relief of pathological pain are sufficient evidence for classification as a morphinelike agent. Recently the use of the Morphine-Benzedrine Group (MBG) scale has improved the methods for assessing morphinelike subjective effects. Substitution studies conducted at various levels of morphine dependence have demonstrated the ability to assess for levels of morphinelike intrinsic activity.

Assessing sedative-hypnotic agents for physical dependence capacity by substitution or direct addiction tests in man is not practical. It appears that from a comparison of secobarbital and pentobarbital, single doses of sedative-hypnotics can be assayed for their ability to facilitate post-rotatory nystagmus and produce scores on scales which measure barbituratelike subjective effects.

474. Jasinski, D.R.: Narcotic antagonists as analgesics of low dependence liability—Theoretical and practical implications of recent studies. In: Brill, L. and Harms, E. (eds.): *The Yearbook of Drug Abuse*, pp. 37–48. New York: Behavioral Publications, 1973.

Evaluation of agents proposed as analgesics of low abuse potential because of their narcotic antagonist activity has indicated that these agents can produce diverse patterns of agonist effects. Nalorphine and cyclazocine produce subjective effects characterized by apathetic sedation and psychotomimetic effects, will not suppress morphine abstinence, will not suppress but will precipitate abstinence in morphine-dependent subjects, and will not produce drug-seeking behavior upon withdrawal after chronic administration. Naloxone, on the other hand, is a pure antagonist which produces no subjective or physiologic changes with acute or chronic administration. Profadol, on the other hand, produces typically morphinelike subjective effects and euphoria, will suppress abstinence in subjects dependent upon 60 mg of morphine per day but will precipitate abstinence in subjects dependent upon 240 mg of morphine per day. With chronic administration, profadol produces typical morphinelike physical dependence. Pentazocine in low doses produced morphinelike subjective effects but in larger doses produced subjective effects which resemble those produced by nalorphine. Pentazocine will precipitate abstinence in subjects dependent upon 240 mg of morphine but unlike profadol will not suppress abstinence in subjects dependent upon 60 mg of morphine daily. With chronic administration pentazocine will produce physical dependence which resembles that produced by both morphine and nalorphine. Most importantly, pentazocine is associated with a degree of drug-seeking behavior. These studies in man support the concept of receptor dualism in which nalorphine exerts its agonistic effects through a receptor different and distinct from that of morphine but it also reacts with the morphine receptor and has little or no activity. Profadol, on the other hand, is felt to be a partial agonist of morphine. Certain drugs such as pentazocine were felt to have agonistic activity at both the morphine and the nalorphine receptors.

475. Jones, B.E. and Prada, J.A.: Relapse to morphine use in dog. *Psychopharmacologia* 30:1–12 (1973).

Intravenous self-administration of morphine by dogs was studied before and during dependence on morphine, and after 1 to 6 months of enforced abstinence. In comparison to pedal response rates during a saline control period, 18 of 22 dogs studied showed decreased rates of responding for morphine during the initial 3-week exposure. Following subsequent passive establishment of dependence in seven dogs, they self-administered morphine and maintained dependence. Following enforced abstinence for periods of 1 to 6 months the seven dogs relapsed to self-administration of morphine when it was again made available. In contrast, additional dogs offered food or amphetamine reinforcements showed marked increases in pedal responding for these reinforcements within a few days after initial exposure. The results indicate that in postdependent dogs that had maintained their dependence on morphine by self-administration, effects other than those experienced during the initial exposure to morphine are responsible for relapse.

476. KAY, D.C.: Civil commitment in the federal medical program for opiate addicts. In: Brill, L. and Harms, E. (eds.): *The Yearbook of Drug Abuse,* pp. 17–35. New York: Behavioral Publications, 1973.

Although not published until 1973, this article reviews the Federal medical program up to January 1969. If briefly describes early civil commitment attempts (the original enabling legislation, *Blue-Grass* commitments, attempts to state commitment to Federal institutions), with the objections which have developed to civil commitment procedures. The 1966 Narcotic Addict Rehabilitation Act is described in detail, with 1969 tabulations of the addict population involved in this program. Problems of the NARA and other addict treatment programs are discussed.

477. KAY, D.C.: Human sleep and EEG through a cycle of methadone dependence. *Electroencephalography and Clinical Neurophysiology* 38:35–43 (1973).

The effects of oral methadone on EEG and sleep were studied in six male postaddicts. Continuous nocturnal measurement of EEG, EMG, and EOG was used to define sleep patterns. Period analysis and power spectral analysis were performed on each 8-min sample of daytime (eyes closed) EEG. Both sleep and EEG were studied during a predrug control period, during the methadone induction phase (45–60 mg/day), stabilization phase (100 mg/day), and then 6, 10, 13, 18, and 22 weeks after withdrawal. One subject did not complete the last two withdrawal sessions. While on methadone, subjects reported that they slept more and also showed an increase in slow wave activity and a decrease in fast wave activity of their EEG during this time. Nocturnal sleep was not markedly altered during the chronic administration of methadone. Subjects

reported an increase in dreaming soon after withdrawal, and then 3–5 weeks of nocturnal insomnia. At the sixth week after withdrawal, slow wave activity in the daytime EEG was decreased, fast wave activity was increased, and mean EEG frequency was increased. REM sleep and delta sleep were increased during withdrawal. These data provide further evidence that chronic administration of narcotic analgesics may induce persistent functional changes in the central nervous system.

478. Kay, D.C.: Sleep and some psychoactive drugs. *Psychosomatics* 14:108–118 (1973).

Morphine in single doses increases wakefulness and drowsiness while decreasing REMS and delta sleep. Partial or complete tolerance to these effects develops after continued morphine administration; however, sleep then precedes and wakefulness follows each drug dosage and bursts of slow wave activity appear in sleep and waking EEG. Withdrawal from methadone in man is associated with an initial increase in dreaming and then several weeks of insomnia during early abstinence, with a decrease in slow wave activity in the waking EEG. Protracted abstinence is characterized by an increase in REM sleep, followed by an increase in delta sleep. Tolerance develops to morphine's initial synchronizing effect on the EEG, leaving a persistent arousal effect from morphine for several months during protracted abstinence. Barbiturate in single doses increases total sleep and EEG spindling while decreasing REM sleep. With continued barbiturate administration, some tolerance probably develops to the effect on REMS, but delta sleep becomes persistently decreased. Withdrawal from barbiturate is associated with insomnia and nightmares, the latter occurring during a marked increase in REM sleep. Delta sleep remains low during chronic barbiturate use and gradually returns to normal levels after withdrawal without known increase above normal. Alcohol and most other sedative-hypnotics appear to have the same general pattern as barbiturate. Both alcohol and barbiturate are associated with a psychosis during withdrawal, which appears to occur during the greatest increase in REMS. Amphetamine in single doses increases wakefulness and decreases all states of sleep. Tolerance apparently develops to these effects, since chronic amphetamine users are reported to have sleep patterns within normal limits. Withdrawal from chronic amphetamine is associated with increased sleep, especially REMS. Amphetamine is also associated with a psychosis during chronic use, which tends to disappear during withdrawal. Most other CNS stimulants appear to have the same general pattern as amphetamine. REM sleep apparently increases during withdrawal from opiates, sedative-hypnotics, or stimulants; psychosis occurs during chronic use of stimulants, but only occurs upon withdrawal from sedative-hypnotics, and does not usually occur either during chronic use

or during withdrawal from opiates. Delta sleep is increased late after withdrawal from opiates and possibly early after withdrawal from stimulants; no increase in delta sleep has yet been described after withdrawal from sedative-hypnotics. However, measures of sleep states apparently are sensitive indicators of CNS homeostasis, and might help to define pharmacologic factors in recurrent drug-seeking behavior.

479. Krivoy, W., Kroeger, D., and Zimmermann, E.: Actions of morphine on the segmental reflex of the decerebrate-spinal cat. *British Journal of Pharmacology* 47:457–464 (1973).

The actions of morphine were studied on the segmental reflex of the decerebrate-spinal cat. Morphine decreased arterial blood pressure. Morphine inhibited mono- and polysynaptic reflexes. The influence of morphine on monosynaptic reflexes was more obvious at stimulation of the dorsal root at a frequency of 12.5 Hz than at 0.5 or 2.5 Hz. The total amount of activity recorded from the ventral root after morphine depended on whether or not the evoked reflex was maximal or submaximal. These actions of morphine were antagonized by naloxone.

480. Krivoy, W. and Zimmermann, E.: A possible role of polypeptides in synaptic transmission. In: Sabelli, H.C. (ed.): *Chemical Modulation of Brain Function. A Tribute to J.E.P. Toman,* pp. 111–121. New York: Raven Press, 1973.

We have briefly indicated Dr. Toman's influence on our thinking. The information reviewed suggests that SP, ACTH, β-MSH, and BK are neurohumors, and that their action on the nervous system is that of modulation, perhaps altering the central excitatory state. Much information is still needed to establish the neurohumoral role of these endogenous polypeptides, including the testing of specific antagonists of their action on nerve recovery processes. Because LSD, MS, and CPZ are known to alter the period of supernormality which follows nerve excitation, an hypothesis based on their interaction with polypeptides is advanced which might explain at least part of the diverse phenomena observed subsequent to their administration.

481. Martin, W.R.: Assessment of the abuse potentiality of amphetamines and LSD-like hallucinogens in man and its relationship to basic animal assessment programs. In: Goldberg, L. and Hoffmeister, F. (eds.): *Bayer-Symposium IV: Psychic Dependence,* pp. 146–155. Berlin-Heidelberg-New York: Springer-Verlag, 1973.

We have every reason to be optimistic about our ability to identify substances which have abuse potentialities similar to that of amphetamine and LSD. In man, we have at hand questionnaires which will measure their ability to produce euphoria, anxiety, and perceptual

distortion. Further, many of the salient features of their physiologic and central nervous system actions have been characterized. Finally, the use of the phenomena of tolerance and cross-tolerance has been shown to be useful and specific in comparing hallucinogens of the LSD type in both man and animals. At the present time, there are insufficient data to know if the demonstration of tolerance and cross-tolerance will be a useful way of identifying amphetaminelike agents; however, these phenomena hold promise and their use should be explored.

482. MARTIN, W.R.: Drug abuse—The need for a rational pharmacologic approach. In: Brill, L. and Harms, E. (eds.): *The Yearbook of Drug Abuse*, pp. 1–15. New York: Behavioral Publications, 1973.

The history of the development of narcotics, depressants, stimulants, and hallucinogens is reviewed and the impact of the rapidly developing pharmaceutical industry on public health is emphasized, as well as the economic and social consequences. Further, the legal and pharmacologic considerations in identifying drugs of abuse are outlined.

483. MARTIN, W.R.: Narcotic analgesics. *British Journal of Hospital Medicine* pp. 175–178 (August 1973).

The general pharmacology and toxicology of narcotic analgesics are reviewed and their agonistic actions discussed. The existence of partial agonists and agonists of the nalorphine type is discussed and how they relate to therapy. The pharmacology of dextropropoxyphene and pentazocine are discussed in some detail.

484. MARTIN, W.R., JASINSKI, D.R., HAERTZEN, C.A., KAY, D.C., JONES, B.E., MANSKY, P.A., and CARPENTER, R.W.: Methadone—a reevaluation. *Archives of General Psychiatry* 28:286–295 (1973).

Methadone hydrochloride produces subjective changes similar to those produced by heroin and is approximately equipotent to morphine when both are administered subcutaneously and one-half as potent when administered orally. Chronically administered methadone produces sedation, lethargic apathy, reduction in sexual interest and activity, hemodilution, and edema. Even when patients were receiving and tolerant to 100 mg/day, drug-seeking behavior was seen. Methadone hydrochloride in dose level of 100 mg orally produces physical dependence similar to that produced by morphine, except that onset of the abstinence syndrome is slower. The abstinence syndrome may be of moderate or severe intensity and is qualitatively similar to morphine abstinence syndrome. As in morphine-dependent subjects, the acute abstinence syndrome of methadone-dependent subjects is followed by a protracted abstinence syndrome.

485. Martin, W.R., Jasinski, D.R., and Mansky, P.A.: Naltrexone, an antagonist for the treatment of heroin dependence. *Archives of General Psychiatry* 28:784–791 (1973).

Naltrexone (EN–1639A) is approximately 17 times more potent than nalorphine as an antagonist in man. It is virtually devoid of agonistic activity, including the ability to induce nalorphinelike dysphoric effects. Its duration of action is longer than that of naloxone, but shorter than that of cyclazocine. It is effective orally. When administered in a dose level of 50 mg/day, it produces a degree of blockade of the effects of morphine and heroin that is comparable to that obtained with 4 mg of cyclazocine per day orally. Naltrexone, thus, appears to be a relatively pure potent narcotic antagonist which is effective orally and which may have utility in the treatment of heroin and narcotic dependence.

486. Thompson, W.O. and Christian, S.T.: Calculating rate constants in forward drug transfer reactions. *Journal of Pharmaceutical Sciences* 62:328–330 (1973).

A simple method for obtaining and processing drug transfer data derived from in vitro model cells such as the Schulman cell is presented. Simplified calculation procedures are developed for determining the rate constants that describe the transfer of the drug through the compartments. Transfer of the acidic drug salicylic acid from a pH 2.0 compartment through a lipid phase to a pH 7.4 compartment was utilized as the test system and example for the method. Theoretical versus experimental transfer curves are presented, along with statistical considerations for data of this type.

487. Vaupel, D.B. and Martin, W.R.: Interaction of oxotremorine with atropine, chlorpromazine, cyproheptadine, imipramine and phenoxybenzamine on the flexor reflex of the chronic spinal dog. *Psychopharmacologia* 30:13–26 (1973).

The central antimuscarinic actions of several drugs, atropine, phenoxybenzamine, cyproheptadine, imipramine, and chlorpromazine, were determined by their ability to antagonize oxotremorine-induced facilitation of the electrically evoked flexor reflex and production of the stepping reflex in the chronic spinal dog. The drug actions and interactions were determined by sequentially infusing the antagonist, methylatropine and oxotremorine and observing changes in flexor reflex amplitude. The facilitation of the flexor reflex and evocation of the stepping reflex produced by oxotremorine in the methylatropine pretreated animal are thought to be due to a direct action on the spinal cord. Atropine, cyproheptadine, imipramine, and chlorpromazine depressed the amplitude of the flexor reflex and phenoxybenzamine produced a slight enhancement. The interaction

studies demonstrated that atropine almost completely prevented the spinal cord effects of oxotremorine while phenoxybenzamine showed no antagonism. Imipramine, chlorpromazine, and cyproheptadine demonstrated the same relative degree of partial antagonism and antimuscarinic activity in the spinal cord. These findings suggest that facilitatory muscarinic cholinergic neurons may be present either as a parallel pathway in the segmental reflex or longitudinally oriented pathways in the spinal cord.

488. Yeh, S.Y.: Separation and identification of morphine and its metabolites and congeners. *Journal of Pharmaceutical Sciences* 62:1827–1829 (1973).

Morphine and its known and postulated metabolites and congeners, i.e., morphine N-oxide, normorphine, pseudomorphine, morphine-N-methyl iodide, codeine, norcodeine, morphine-3-glucuronide, and morphine ethereal sulfate, were separated by TLC and GLC. The R_f values of nalorphine and nicotine and its metabolites and the retention times of nalorphine and seven other chemicals commonly used for GLC quantitative determination of morphine and codeine are also presented.

489. Yeh, S.Y., Flanary, H., and Sloan, J.: Efficient, low-cost gas manifold for use in sample concentration. *Clinical Chemistry* 19:687–688 (1973).

The construction of an efficient, low-cost manifold for use in sample concentrations was described.

490. Yeh, S.Y. and Gorodetzky, C.W.: The effect of pargyline on the toxicity of morphine in the rat. *Toxicology and Applied Pharmacology* 24:387–392 (1973).

The effect of pargyline on the toxicity of morphine in rats has been investigated. The toxicity of morphine 4 h after an acute ip injection of pargyline is significantly increased. The toxicity of morphine in rats receiving morphine 4 or 24 h after the sixth daily ip injection of pargyline is significantly decreased when compared to the acutely pargyline-treated animals. However, the toxicity of morphine is still increased in these animals when they are compared to saline-treated groups. The animals first lost weight 24–48 h following the administration of pargyline, then gained weight with a slower rate as compared to those receiving saline.

491. Zimmermann, E. and Krivoy, W.: Antagonism between morphine and the polypeptides ACTH, $ACTH_{1-24}$, and β-MSH in the nervous system. In: Zimmermann, E., Gispen, W.H., Marks, B.H. and de Wied, D. (eds.): *Drug Effects on Neuroendocrine Regulation*, Progress in

Brain Research, Vol. 39, pp. 383–394. Amsterdam: Elsevier Publishing Co., 1973.

The information reviewed illustrates that the peptides, ACTH, $ACTH_{1-24}$, and β-MSH, can antagonize the depressant action of morphine on the central nervous system. The mechanism underlying this antagonism is not known, although the antagonism has been demonstrated to occur at the spinal cord level. Based upon evidence that morphine decreases, whereas β-MSH increases the period of supernormality following detonation of the nerve cell, the possibility is discussed that these agents exert opposing actions on synaptic transmission, and thereby modulate the central excitatory state in opposite directions. Although much more evidence is needed to critically evaluate this hypothesis, it might help explain, in part at least, the development of tolerance to morphine.

1974

492. Bell, J.A. and Martin, W.R.: Studies of tryptamine and lysergic acid diethylamide (LSD) on cutaneous C-fiber and polysynaptic reflexes in the cat. *The Journal of Pharmacology and Experimental Therapeutics* 190:492–500 (1974).

The superficial peroneal nerve of the acute decerebrate spinal (L_1) cat was stimulated with a voltage and duration maximal for C-fiber activation. Short latency polysynaptic reflexes (PSR) and long latency C-fiber reflexes (CFR) were recorded from an ipsilateral S_1 ventral root. Both the PSR and the integral of the CFR were recorded on tape and averaged using a PDP–12 computer. Infusions of tryptamine at a rate of 0.5 mg/kg/min for 10 minutes increased the CFR to a mean of 308 percent (S.E.M.±37.3 percent) of control and the PSR to a mean of 125 percent (S.E.M.±5.7 percent) of control. The facilitation by tryptamine was antagonized by cyproheptadine 0.5 mg/kg. Lysergic acid diethylamide (LSD) infused at a rate of 0.375 μg/kg/min for 40 minutes produced facilitation of the CFR which reached a maximum of 297 percent of control (S.E.M.±43.7 percent) 60 minutes postinfusion. Facilitation of the PSR by LSD was significant only immediately postinfusion (110 percent control). The facilitation of the CFR by LSD was partially antagonized by cyproheptadine, 0.5 mg/kg. Methysergide, 0.4 mg/kg, had a biphasic action on the CFR, producing an initial depression followed by facilitation. Tryptamine infusion produced a significant depression of the CFR after methysergide pretreatment. LSD produced no further increase in the CFR after facilitation produced by methysergide. These studies demonstrated that tryptamine and LSD have a

similar mode of action on spinal cord CFR, and that tryptamine and LSD produce a greater facilitation of the CFR than the short-latency PSR.

493. Cone, E.J., Gorodetzky, C.W., and Yeh, S.Y.: The urinary excretion profile of naltrexone and metabolites in man. *Drug Metabolism and Disposition* 2:506–512 (1974).

The urinary excretion pattern of free and conjugated naltrexone and the metabolite 6-β-hydroxynaltrexone was determined for six human subjects for a period of 6 days after oral administration of 50 mg of naltrexone. The levels of free and conjugated drug and metabolite were determined by a gas-chromatographic analysis procedure using naloxone as an internal standard and by correlating peak height ratios to concentration. The mean excretions ± SE of free naltrexone and 6-β-hydroxynaltrexone were estimated as 1.2±0.2 and 26.3±2.2 percent of administered dose, respectively. The mean excretions of conjugated naltrexone and metabolite were estimated as 9.7 and 16.4 percent of administered dose, respectively. The timed urinary excretion profile indicated that naltrexone is metabolized and excreted rapidly (mean excretion $t_{1/2}$=1.1h), whereas the free metabolite, 6-β-hydroxynaltrexone, persists at detectable levels for 6 days (mean excretion $t_{1/2}$= 14–18 h). Preliminary dose-ranging studies of 6-β-hydroxynaltrexone in the chronic spinal dog suggest antagonistic activity of the metabolite.

494. Gorodetzky, C.W.: Assays of antagonistic activity of narcotic antagonists in man. In: M.C. Braude, L.S. Harris, E.L. May, J.P. Smith and J.E. Villarreal (eds.): *Narcotic Antagonists,* Advances in Biochemical Psychopharmacology, Vol. 8, pp. 291–297. New York: Raven Press, 1974.

This chapter reviews the methods which have been developed and briefly summarizes the results which have been obtained for evaluation of the antagonistic actions of narcotic antagonists in man over approximately the last 10 years at the NIMH Addiction Research Center. The major assay procedure is the precipitation test. Single doses of narcotic antagonist are administered to subjects dependent on 60 or 240 mg of morphine per day, and abstinence is quantitatively evaluated over the next 3 h using a modification of the method of Himmelsbach. By using two doses each of a standard antagonist (nalorphine) and a test antagonist, relative potency for precipitation of abstinence can be determined using the design and statistics for a four-point parallel line bioassay. Relative potencies published to date (expressed as mg=1 mg of nalorphine) have been determined as follows: (1) using subjects dependent on 240 mg/day morphine: naloxone, 0.14; cyclazocine, 0.18; levallorphan, 0.52; nalorphine, 1.00; profadol, 43.5; pentazocine, 51.2; propiram, 192; (2) using subjects dependent on 60 mg/day morphine:

naloxone, 0.10; nalorphine, 1.00; nalbuphine, 3.7. To evaluate duration of action, a single dose of narcotic antagonist (or placebo) is administered at various intervals prior to a standard test dose of morphine, the effects of which are measured on pupillary diameter and parameters of the standard single-dose opiate questionnaire. Published results have shown antagonistic actions of naloxone to last at least 9 h and cyclazocine for 12 to 24 h. To assess the antagonistic actions of narcotic antagonists during their chronic administration, single test doses of opiate have been administered prior to and then during chronic antagonist administration. In addition, during chronic antagonist administration, morphine at 240 mg/day has been chronically administered, then abruptly withdrawn under double-blind conditions, and abstinence quantitatively evaluated by the method of Himmelsbach. Results have shown that chronically administered narcotic antagonists maintain their ability to block the effects of single doses of narcotic analgesics and to antagonize the development of physical dependence on chronically administered morphine.

495. Gorodetzky, C.W., Angel, C.R., Beach, D.J., Catlin, D.H., and Yeh, S.Y.: Validity of screening methods for drugs of abuse in biological fluids. I. Heroin in urine. *Clinical Pharmacology and Therapeutics* 15:461–472 (1974).

In evaluating methods of detecting drugs of abuse in biological fluids it is of special importance to determine the ability of detecting a drug or its metabolites in biological fluids. To evaluate several methods of detecting heroin use by urine analysis for morphine and its metabolites, single intravenous doses of 2.5 and 5 mg/70 kg heroin were administered a week apart in random order to 10 nontolerant subjects and their urine was collected for the week following. Along with predrug control urines, each sample was coded, randomized, and analyzed under blind conditions by the following methods: (1) thin-layer chromatography (TLC) with iodoplatinate preceded by each of four extraction procedures, organic solvent and ion-exchange resin impregnated paper extraction both without and with prior acid hydrolysis; (2) the free radical assay technique (FRAT); (3) radioimmunoassay (RIA); and (4) the Technicon Autoanalyzer. There was a high probability of detection for the first 8 hours by all methods except the Technicon Autoanalyzer (which gave a low proportion of positives 8 hours after the 2.5 mg per 70 kg heroin dose); up to 16 hours with TLC procedures with hydrolysis and FRAT; and up to 32 to 48 hours with RIA.

496. Gorodetzky, C.W. and Kullberg, M.P.: Validity of screening methods for drugs of abuse in biological fluids. II. Heroin in plasma and saliva. *Clinical Pharmacology and Therapeutics* 15:579–587 (1974).

Five subjects received 3 single intravenous doses of heroin, 2.5, 5, and 10 mg per 70 kg and 1 oral dose of dextromethorphan, 60 mg per 70 kg; another four subjects received morphine, 30 mg, subcutaneously, four times per day for 3 months. Saliva and plasma samples were collected at intervals for 48 hours following each single drug dose and hourly for 6 hours between chronic doses. Plasma samples were analyzed for opiate by RIA, and saliva samples by RIA, a modified FRAT, and the EMIT. The low dose of heroin was not consistently detectable at any sampling time in either the plasma or the saliva. The medium and high doses were detectable with high probability for 2 to 4 hours in plasma and 1 to 2 hours in saliva. Dextromethorphan was not detectable in plasma but was detected with high probability in saliva for 30 minutes by EMIT and 2 hours by FRAT. During chronic administration there were high probabilities of detection of morphine in plasma for at least 6 hours and in saliva for 3 to 4 hours after the last morphine dose. While these fluids do not appear to be as useful as urine in routine screening for heroin, they may be useful in the detection of high-dose chronic abuse.

497. Haertzen, C.A.: An overview of Addiction Research Center Inventory (ARCI): An appendix and manual of scales. DHEW Publication No. (ADM) 74–92, 1974.

The main purposes of this review and manual are to provide the ARCI user with the 38 most valid scales, a quantitative method for characterizing the similarity of a profile of scores for the subject, group, or experimental condition with those found for 10 experimental drug conditions and 6 psychiatric groups, a comprehensive listing of average test scores of all experimental conditions or groups tested, and the degree of similarity of the profile of scores for these conditions or groups with those found for 10 drug conditions and 6 psychiatric categories. The manual provides some details on the history of the test, scoring, T-score transformation of scores, internal consistency and reliability of scales, and the validity of the scales for a number of purposes. The most useful information on a group or condition tested is the average scores on the 38 recommended scales as these averages can serve as a standard for comparison in classification of subjects or groups. To maximize the accessibility of the average scores on 38 scales, all conditions and groups which have been tested on the whole ARCI have been assigned condition numbers. Studies have shown that there are differences among 6 psychiatric groupings and among 10 drug conditions. These groups or conditions have also been assigned numbers. The condition identification numbers for the 10 experimental drug conditions determined in opiate addicts are: no-drug (00+91), morphine (20), combined conditions for cyclazocine and nalorphine (23+25), pen-

tobarbital (31), chlorpromazine (40), LSD (51), benzedrine (60), alcohol (81), conditions for opiate withdrawal (154 +168), conditions for chronic opiate effects (151 +152 +153). The six psychiatric groups are: Mentally ill groups (26 +27), normals (28), alcoholics (86 +87 +88), criminals (94), opiate addicts (170 +173), and simulated mental illness determined in opiate addicts (307). These experimental drug conditions and groups as well as others have been placed in alphabetical order in the index for conditions and groups along with their identification numbers. These identification numbers have been applied in the text and must be used to find the descriptive information about conditions and their average scores (appendix table 3), and the results of a similarity-dissimilarity index with the 10 experimental drug conditions and the clinical groups (appendix table 4). The manual, for the most part, presents results only when the total test has been given. In numerous pharmacological studies short forms or single scales of the ARCI have been used. In order to make this body of information available to the researcher, all references are given in which the whole test or part of the test has been used. In the subject index all of the drugs which have been used in the studies (even though not mentioned in the text) are referred to by reference number. For instance, levallorphan has been cited in references 37 and 66, but not in the text. It is thought that the ARCI appendix of average scores on 38 scales should be periodically updated in order to make the ARCI maximally useful. This objective can be achieved if users will provide the author with the mean raw scores or actual test papers on any groups which they have tested. Actual test papers are of further interest for assessing results on additional scales that may be developed in the future.

498. HAERTZEN, C.A.: Subjective effects of narcotic antagonists. In: M.C. Braude, L.S. Harris, E.L. May, J.P. Smith, and J.E. Villarreal (eds.): *Narcotic Antagonists, Advances in Biochemical Psychopharmacology*, Vol. 8, pp. 383–398. New York: Raven Press, 1974.

The two symptoms, tiredness and drunkenness, which are the most frequently reported acute effects of the narcotic antagonists nalorphine and cyclazocine are also typical actions of barbiturates and alcohol. Psychotomimetic effects also occur in the antagonists, but somewhat less frequently. The overall pattern is different from the psychotomimetic drug LSD, which produces more psychotomimetic symptoms, anxiety, and excitement, less drunkenness, and no sedation. In common with opiates, the two antagonists produce analgesia. Euphoria is a pronounced acute effect of opiates, but not of the antagonists. At low doses, opiate addicts express some liking for the antagonists, but this effect drops off with higher doses. The similarity of a drug's subjective agonistic effects with those of nalorphine or morphine is associated with the drug's power to either precipitate or suppress abstinence symptoms in

opiate addicts stabilized on morphine. Predictions of suppression or precipitation cannot be reliably made with drugs which have no agonistic effects. The acute effects of cyclazocine are antagonized by naloxone according to Jasinski, Martin, and Sapira. Resnick, Fink, and Freedman found that naloxone lessened the occurrence of undesirable effects of cyclazocine. Tolerance develops to the agonistic subjective effects of the antagonists upon chronic administration, but not to the antagonistic action. The most frequently occurring abstinence symptoms following withdrawal of the antagonists in a study of opiate addicts by Martin et al., were restlessness, sleeplessness, nausea, headaches, bad dreams, chills, and shocks, but drug-seeking did not occur. Yawning, perspiration, rhinorrhea, gooseflesh, and diarrhea were also observable.

499. Haertzen, C.A., Hooks, N.T., Jr., and Pross, M.: Drug associations as a measure of habit strength for specific drugs. *Journal of Nervous and Mental Disease* 158:189–197 (1974).

Several forced choice association studies with opiate addicts and normals were undertaken to test the hypothesis that some portion of associations between words and a drug is based on accumulated habit strength for a drug. Heroin addicts generally associated more words to heroin than to benzedrine, alcohol, goofballs (barbiturates), or reefers (marihuana). The tendency was most marked on words regarded as relevant for drugs such as take, custom, high, hide, buy, and habit. Heroin addicts gave more heroin associations to drug-relevant words than did normals. Addicts who had been experimentally addicted to methadone associated more words to methadone than those who did not have the experience. Individual differences in heroin associations were correlated with those for morphine, but not for methadone in spite of the similarity in the subjective effects of these drugs.

500. Jasinski, D.R., Nutt, J.G., and Griffith, J.D.: Effects of diethylpropion and *d*-amphetamine after subcutaneous and oral administration. *Clinical Pharmacology and Therapeutics* 16:645–652 (1974).

The effects of diethylpropion were determined and compared with those of *d*-amphetamine in nine subjects using a crossover design. Diethylpropion produced effects qualitatively similar to those of *d*-amphetamine, but significantly less potent. Orally diethylpropion was $1/6^{th}$ to $1/11^{th}$ as potent as *d*-amphetamine while subcutaneously diethylpropion was 1/10th to 1/20th as potent as *d*-amphetamine. A striking difference between diethylpropion and *d*-amphetamine was the relatively greater oral efficacy of diethylpropion. Diethylpropion was twice as potent orally as subcutaneously while oral and subcutaneous *d*-amphetamine were equipotent.

501. Krivoy, W.A., Kroeger, D., Taylor, A.N., and Zimmermann, E.: Antagonism of morphine by β-melanocyte-stimulating hormone and by tetracosactin. *European Journal of Pharmacology* 27:339–345 (1974).

Using the decerebrate-spinal Lloyd preparation morphine depressed evoked mono- and polysynaptic reflex activity, β-melanocyte-stimulating hormone enhanced monosynaptic reflex activity, and tetracosactin had no effect. When morphine injection was preceded either by β-melanocyte-stimulating hormone or by tetracosactin a statistically significant depression was not observed. The stimulant actions of β-melanocyte-stimulating hormone did not appear to account for its capacity to antagonize morphine. The fall of blood pressure which follows the administration of morphine in this preparation was not antagonized by the prior administration of either polypeptide.

502. Krivoy, W.A., Zimmermann, E., and Lande, S.: Facilitation of development of resistance to morphine analgesia by desglycinamide^{9}-lysine vasopressin. *Proceedings of the National Academy of Sciences of the United States of America* 71:1852–1856 (1974).

Desglycinamide^{9}-lysine vasopressin facilitates development of resistance to the analgesic action of morphine in mice if morphine is administered before the peptide. Desglycinamide^{9}-lysine vasopressin is not a morphine antagonist, and does not appear to cause either hyperalgesia or alteration of the response to the technique used for evaluating analgesia.

503. Kullberg, M.P. and Gorodetzky, C.W.: Studies on the use of XAD–2 resin for detection of abused drugs in urine. *Clinical Chemistry* 20:177–183 (1974).

We describe a procedure for extracting weakly acidic, neutral, and basic drugs from urine by using a column of XAD-2 resin. Adsorption of drugs from 20 ml of urine buffered at pH 8.5±0.5 at a controlled flow rate of 2.5 ml/min was greater than 89 percent for all drugs tested except aspirin. On eluting the drugs tested with acetone and methanol/chloroform, recoveries ranged from 75 to 93 percent. Overall recoveries of drugs from urine to a thin-layer chromatography plate were between 63 and 78 percent. The concentration of morphine added to normal urine that can be detected 99 percent of the time (95 percent confidence limits) by this method was 80 (65–100) μg/liter. We evaluated three methods for recovering morphine from morphine glucuronide added to urine, by using appropriate modifications of the XAD-2 resin extraction method. Hydrolysis of urine, hydrolysis of urine extracts adsorbed on XAD-2 resin, and hydrolysis of urine extracts from the XAD-2 resin followed by a solvent extraction gave 75 percent, 40 percent, and 10 percent recoveries of morphine, respectively.

504. Martin, W.R., Eades, C.G., Thompson, W.O., Thompson, J.A., and Flanary, H.G.: Morphine physical dependence in the dog. *The Journal of Pharmacology and Experimental Therapeutics* 189:759–771 (1974).

A convenient procedure for making chronic spinal dogs physically dependent on morphine and maintaining them for many months has been described. Both the precipitated and withdrawal abstinence syndromes have been qualitatively described and quantitatively assessed and appear to be qualitatively different. The qualitative characteristics of the precipitated abstinence syndrome appear to depend on the level of dependence, whereas the withdrawal abstinence syndrome does not. The dependent spinal dog was used to assay the relative potencies of antagonists in precipitating abstinence. Good agreement was obtained between comparable data in man and estimates of antagonistic potencies obtained using the guinea pig ileum. Morphine suppresses the withdrawal abstinence syndrome in a dose-related manner. Haloperidol was found to suppress certain signs of abstinence, but not others. Propranolol neither suppressed nor precipitated abstinence. The primary abstinence syndrome, characterized by increased pulse rate, pupillary diameter, respiratory rate, and responsivity to nociceptive stimuli, became maximal on the 2d day of withdrawal abstinence and persisted for about 1 week. A protracted syndrome then emerged characterized by a decrease in body temperature, slowing of pulse and respiratory rate, shortening of the latency of the skin twitch reflex, decreased responsivity of the flexor reflex to a low level of noxious stimuli, and increased responsivity to medium and high strengths of stimuli. The relationship between these findings and exacerbation of the psychopathic personality as a consequence of narcotic addiction is discussed.

505. Martin, W.R. and Sandquist, V.: A sustained release depot for narcotic antagonists. *Archives of General Psychiatry* 30:31–33 (1974).

A total of 175 mg of naltrexone monohydrate, suspended in small particles of a polylactide plastic (500 mg), was injected intramuscularly in dogs whose spinal cords had been transected at the T5–10 levels. This produced a level of blockade against the effects of morphine (1 mg/kg) on the flexor and skin twitch reflex and pupillary diameter for a duration of 21 to 29 days. In some instances levels of blockade could still be detected 33 days after administration. This preparation demonstrates the feasibility of a slow release form of a narcotic antagonist that may have value in the treatment of narcotic addicts.

506. Martin, W.R. and Sloan, J.W.: The possible role of tryptamine in brain function and its relationship to the actions of LSD-like hallucinogens. *The Mount Sinai Journal of Medicine* 41:276–282 (1974).

The history of the development of the concept that LSD-like hallucinogens are tryptaminergic agonists and the demonstration of the role of tryptamine in brain function is recounted. The similarities of the mode of action of LSD-like hallucinogens and tryptamine in the chronic spinal dog are described and the fact that these agents can be differentiated through the use of antagonists from noradrenergic and cholerinergic agonists as well as from amphetamine and 5-hydroxytryptophan. The demonstration that tryptamine produced LSD-like effects in man and that chronic spinal dogs tolerant to LSD were cross tolerant to tryptamine provided additional evidence of the similarity of modes of action of these drugs. Demonstrating the presence of tryptamine in the brains of rats, dogs, steer, and man further supports the concept that tryptamine is a neurotransmitter. The possible role of tryptamine in normal and pathologic functioning of the brain is discussed.

507. MARTIN, W.R., SLOAN, J.W., BUCHWALD, W.F., and BRIDGES, S.R.: The demonstration of tryptamine in regional perfusates of the dog brain. *Psychopharmacologia* 37:189–198 (1974).

Several regions of the pentobarbital-anesthetized dog brain of less than 1 mm^3 in volume were perfused using a modified Gaddum push-pull cannula. Tryptamine was recovered from perfusates of the cerebral cortex, hippocampus, caudate, thalamus, and hypothalamus and was released at a rate of about 0.1 ng/min. The mean blood concentration of tryptamine was approximately 7 ng/ml. Isocarboxazid pretreatment did not increase the amount of tryptamine in the perfusate.

508. MARTIN, W.R., THOMPSON, W.O., and FRASER, H.F.: Comparison of graded single intramuscular doses of morphine and pentobarbital in man. *Clinical Pharmacology and Therapeutics* 15:623–630 (1974).

Graded single intramuscular doses of morphine sulfate (8, 16, and 32 mg) and pentobarbital sodium (150, 200, and 250 mg) and a placebo were administered double blind to 12 nontolerant narcotic addicts. To assess the magnitude and time course of subjective effects and associated signs, "single and chronic dose" opiate questionnaires were completed by subjects and observers. Objective measurements of drug effect were concurrently made, using photographs of the pupils and the duration of postrotational nystagmus. Overall, the questionnaires showed definite and different constellations of symptoms and signs for morphine and pentobarbital. Objective measurements were also different. Morphine induced a dose-related decrease in pupillary diameter and an increase in the signs scratching, relaxed, coasting, talkativeness, and conjunctival injection and caused relaxation, talkativeness, and turning of the stomach. Pentobarbital induced a dose-related increase in the

duration of postrotational nystagmus and caused sleepiness and drunkenness. Both drugs induced euphoria.

509. Mulé, S.J., Gorodetzky, C.W., and Clements, T.H.: Disposition and metabolism of ^{3}H-cyclazocine in dogs. In: Braude, M.C., Harris, L.S., May, E.L., Smith, J.P., and Villarreal, J.E. (eds.): *Narcotic Antagonists,* Advances in Biochemical Psychopharmacology, Vol. 8, pp. 503–523. New York: Raven Press, 1974.

The metabolism of ^{3}H-cyclazocine was studied in nontolerant, tolerant, and abstinent dogs after a 1.25 mg/kg (free base) s.c. injection of the drug. Norcyclazocine and cyclazocine were identified in the urine of these dogs after extraction and direct application of hydrolyzed and unhydrolyzed urine samples to chromatographic paper buffered with 0.1 M phosphate or impregnated with silicic acid. The chromatograms were developed with tertiary amyl alcohol-n-butyl ether-water (80:7:13, v/v) or ethyl acetate-methanol-NH_4OH(85:10:5, v/v). Methods were developed for the estimation of ^{3}H-norcyclazocine in biologic material with a minimal sensitivity of 3 ng/ml. The mean percentage recovery of the administered dose of ^{3}H-cyclazocine obtained from urine and feces for both free and conjugated drug over a period of 120 hr was 43.7 percent from nontolerant dogs, 58.5 percent from tolerant dogs, and 40.7 percent from abstinent dogs. In the urine of nontolerant, tolerant, and abstinent dogs, 2.3 to 2.7 percent of the ^{3}H-cyclazocine was recovered as free norcyclazocine and an equal amount as conjugated norcyclazocine. In the feces of these dogs, from 1.5 to 2.4 percent of the free and 0.02 to 0.7 percent of the conjugated norcyclazocine was obtained. Norcyclazocine was not found in the brain of the dogs at various time intervals, but the metabolite was obtained in peripheral tissues. No drug was found in the CNS of a 24-h abstinent dog. Urine samples were subjected to acid and enzymatic hydrolysis, using β-glucuronidase and phenol sulfatase. The data indicated that the conjugate of both cyclazocine and norcyclazocine was a glucuronide. The results indicated that potency of cyclazocine but not latency of abstinence was correlated with distribution. Norcyclazocine (1.0 mg/kg) did not significantly depress the flexor reflex of the chronic spinal dog. It is concluded that norcyclazocine is not an active metabolite of cyclazocine and that 47 to 66 percent of the administered ^{3}H-cyclazocine was accounted for as free and conjugated cyclazocine and norcyclazocine, as determined over a 5-day period.

510. Nutt, J.G. and Jasinski, D.R.: Diuretic action of the narcotic antagonist oxilorphan. *Clinical Pharmacology and Therapeutics* 15:361–367 (1974).

The narcotic antagonists oxilorphan and *d,l*-cyclazocine increased urinary output without affecting fluid intake in 10 subjects on ad libitum

fluids. In eight water-deprived subjects oxilorphan increased urinary output and decreased urine osmolality without significantly altering blood pressure, creatinine clearance, electrolyte excretion, or solute excretion. Three of four water-loaded subjects excreted a water load slightly more efficiently after the drug. Ten milligrams of naloxone had no diuretic effect itself and did not antagonize the diuretic effect of oxilorphan. Five units of vasopressin prevented the drug-induced diuresis. These results suggest that the diuretic effect is an agonistic action of oxilorphan produced by inhibition of antidiuretic hormone (ADH) release.

511. Nutt, J.G. and Jasinski, D.R.: Methadone-naloxone mixtures for use in methadone maintenance programs. I. An evaluation in man of their pharmacological feasibility. II. Demonstration of acute physical dependence. *Clinical Pharmacology and Therapeutics* 15:156–166 (1974).

It has been proposed that mixtures of methadone and the narcotic antagonist, naloxone, be substituted for the methadone dispensed in methadone maintenance programs to reduce methadone diversion. By the oral route in nondependent subjects methadone-naloxone mixtures are indistinguishable from methadone alone. By the parenteral route, the mixtures have significantly less miotic, behavioral, and subjective effects than methadone alone. Administration of methadone with naloxone to morphine-dependent subjects ameliorates but does not abolish the abstinence precipitated by the naloxone. Ten milligrams of naloxone administered orally does not precipitate abstinence in morphine-dependent subjects, and doses of 15 and 30 mg produce only mild signs of abstinence. It is concluded that methadone-naloxone mixtures could be compounded that would be interchangeable with methadone intended for oral consumption, but have less parenteral abuse liability than methadone. The observation that 4 mg of parenterally administered naloxone precipitated signs of abstinence 1 week after a single dose of methadone indicated the development of acute physical dependence on methadone.

512. Sahai, H. and Thompson, W.O.: Comparisons of approximations to the percentiles of the t,x^2, and F distributions. *Journal of Statistical Computation and Simulation* 3:81–93 (1974).

Approximations for the percentiles at arbitrary levels of the t,x^2, and F distributions can be found in the literature, but with little information about the accuracy. This paper provides a single source of these approximations and contains tables of percent errors to aid in the selection of the simplest procedure yielding the required accuracy. For use in digital computers, approximations compared in this paper yield percentiles more rapidly than more exact iteration schemes with accu-

racy dependent on the complexity of the approximation. An approximation procedure may also be used to obtain percentiles for nonintegral degrees of freedom.

513. Yeh, S.Y. Absence of evidence of biotransformation of morphine to codeine in man. *Experientia* 30:265–266 (1974).

The content of codeine in morphine sulfate, U.S.P., has been determined with GLC and found to be 0.04 percent. The amount of codeine found in the urine of morphine-dependent subjects (on 240 mg morphine sulfate per day) was about 31.1 percent of the codeine present as impurity in the administered morphine sulfate. The observation of codeine in the urine of morphine addicts, therefore, could be accounted for by contamination of the injected morphine sulfate.

514. Zimmermann, E. and Krivoy, W.: Depression of frog isolated spinal cord by morphine and antagonism by tetracosactin. *Proceedings of the Society for Experimental Biology and Medicine* 146:575–579 (1974).

The purpose of these experiments was to determine if tetracosactin ($ACTH_{1-24}$) will antagonize the actions of morphine (MS) on neural tissue isolated from other body systems. The monosynaptic ventral root response (MVR) of frog isolated spinal cord in vitro was used to test this question. In this preparation MS produces a depression of MVR which is antagonized by naloxone, by $CaCl_2$, and by decreased temperature. $ACTH_{1-24}$ did not alter MVR, but did antagonize the actions of MS.

1975

515. Cone, E.J. and Gorodetzky, C.W.: Analytical controls in drug metabolic studies. A commentary. *Drug Metabolism and Disposition* 3:417–418 (1975).

With the increasing use of highly sensitive and specific analytical techniques larger numbers of qualitatively minor metabolites are likely to be described in the drug literature. Therefore, it is imperative that investigators be aware of possible sources of analytical artifacts and include appropriate controls in their procedures to ensure against misinterpretation of analytical data. In this regard an example of artifact production is described for morphine urine in which small amounts of α-isomorphine is produced during the acid-hydrolysis step. Had appropriate controls not been included (in the concentration range of the morphine in the drug-urine) the artifact could have been mislabeled as a metabolite of morphine. Thus, careful selection of controls is necessary and should include analytical processing of predrug control samples

without and with added drug and metabolites (when available) in the concentration range of the naturally occurring drug.

516. Cone, E.J. and Gorodetzky, C.W.: Metabolism of naltrexone and naloxone. *Committee on Problems of Drug Dependence.* Washington, D.C.: National Academy of Sciences, National Research Council, 1975.

Noroxymorphone was detected by chemical ionization GC–MS in the urine of man administered a single oral dose of naltrexone or naloxone and in monkey administered naltrexone chronically 12 mg/kg/day orally. Also, in addition to detecting the parent drug and its 6-β-hydroxy-metabolite, metabolites of naltrexone and naloxone were detected whose apparent molecular weights are consistent with aromatic hydroxylation and hydroxy-methylation to form a catechol type metabolite.

517. Cone, E.J., Gorodetzky, C.W., and Yeh, S.Y.: Biosynthesis, isolation, and identification of 6β-hydroxynaltrexone, a major human metabolite of naltrexone. *Journal of Pharmaceutical Sciences* 64:618–621 (1975).

Chemical reduction of naltrexone is described in an attempt to synthesize 6β-hydroxynaltrexone. Only the epimer, 6α-hydroxynaltrexone, was produced. Pilot metabolic studies on naltrexone in the dog, rat, and guinea pig were made to determine which animal produced the greatest amount of 6β-hydroxynaltrexone. The guinea pig was selected and used to produce the metabolite. Isolation and purification methods are described, and spectral data are presented for structural confirmation of the metabolite.

518. Gilbert, P.E. and Martin, W.R.: Antagonism of the convulsant effects of heroin, *d*-propoxyphene, meperidine, normeperidine and thebaine by naloxone in mice. *The Journal of Pharmacology and Experimental Therapeutics* 192:538–541 (1975).

Naloxone antagonized convulsions produced by tail vein infusions of *d*-propoxyphene, heroin, meperidine, normeperidine, and thebaine in mice in a dose-related manner. Pretreatment with naloxone (60 mg/kg i.p.) produced a 200 percent increase of the dose of *d*-propoxyphene or heroin needed to produce a seizure. A 40 percent increase in the convulsant dose of meperidine was observed after naloxone pretreatment (30 mg/kg i.p.). Naloxone (15 mg/kg i.p.) produced a 30 percent increase in the convulsant dose of normeperidine; however, larger doses of naloxone did not produce any further increase in the convulsant dose of either normeperidine or meperidine. Larger doses of naloxone were needed to antagonize convulsions produced by thebaine. Heroin, *d*-propoxyphene, and meperidine pro-

duced nonlethal clonic seizures, whereas normeperidine and thebaine produced tonic-clonic seizures which were followed by death. These data suggest that there may be two mechanisms by which narcotic analgesics and their congeners produce convulsions.

519. Gorodetzky, C.W. and Kullberg, M.P.: Etorphine in man. II. Detectability in urine by common screening methods. *Clinical Pharmacology and Therapeutics* 17:273–276 (1975).

A single highly euphorigenic dose of etorphine, 100 μg, was administered subcutaneously to seven nontolerant subjects, and all urine samples were collected for 1 day prior to and 3 days following drug administration. Samples were analyzed for the presence of opiates by radioimmunoassay (Abuscreen) and homogeneous enzyme immunoassay (EMIT), with cutoffs for "positives" of 40 and 500 ng/ml, respectively. Samples were analyzed for etorphine by thin-layer chromatography (TLC) with iodoplatinate preceded by XAD-2 resin extraction (sensitivity =0.2 μg etorphine/ml of urine) and by gas-liquid chromatography (GLC) preceded by organic solvent extraction and trimethylsilyl derivatization (sensitivity =0.1 μg etorphine/ml of urine). The last predrug and first two postdrug samples were also analyzed after acid hydrolysis by TLC and after glucuronidase hydrolysis by TLC and GLC. No sample gave a "positive" opiate result in either immunoassay, and no etorphine was detected in the TLC and GLC analyses of any urine sample. Thus, it is unlikely that the abuse of etorphine could be diagnosed by urinalysis using the common screening methods of radioimmunoassay, EMIT, TLC preceded by XAD-2 resin extraction, or GLC preceded by organic solvent extraction and trimethylsilyl derivatization.

520. Gorodetzky, C.W., Martin, W.R., Jasinski, D.R., Mansky, P.A., and Cone, E.J.: Human pharmacology of naltrexone. In: Senay, E., Shorty, V. and Alksne, H. (Eds.): *Developments in the Field of Drug Abuse (National Drug Abuse Conference, 1974),* pp. 749–753. Cambridge: Schenkman Publishing Company, 1975.

In a brief review article the pharmacologic effects of naltrexone in man are summarized. Naltrexone is a potent narcotic antagonist, approximately twice as potent as naloxone and 17 times as potent as nalorphine in precipitating abstinence in morphine-dependent subjects. It is orally effective. A single oral dose of 15 mg produced significant morphine antagonistic effects for 24 hours and chronic administration at dose levels of 30 to 50 mg per day significantly antagonizes both the physical-dependence producing properties and euphorigenic effects of morphine. Chronic oral naltrexone at 50 mg/day is approximately equivalent to 4 mg/day of cyclazocine in attenuating the abstinence syndrome from concomitantly administered chronic morphine. Nal-

trexone has minimal agonistic effects and in doses adequate to produce opiate blockade it is subjectively indistinguishable from placebo. Because of its antagonistic potency, oral effectiveness, duration of action, and lack of agonistic effects, it should offer significant advantages over naloxone and probably cyclazocine in the treatment of heroin dependence.

521. Griffith, J.D., Nutt, J.G., and Jasinski, D.R.: A comparison of fenfluramine and amphetamine in man. *Clinical Pharmacology and Therapeutics* 18:563–570 (1975).

dl-Fenfluramine hydrochloride (60, 120, 240 mg), *d*-amphetamine sulfate (20, 40 mg), and placebo were compared in eight postaddict volunteers, each dose given orally in random sequence at weekly intervals using a double-blind crossover design. Fenfluramine had little effect on blood pressure and temperature, but caused a marked dilation of pupils, whereas amphetamine was a potent vasopressor and a weak mydriatic. While fenfluramine produced euphoria in some subjects, its overall effects were unpleasant, sedative, and qualitatively different from amphetamine. Three subjects given 240 mg of fenfluramine experienced brief but vivid hallucinogenic episodes characterized by olfactory, visual, and somatic hallucinations, abrupt polar changes in mood, time distortion, fleeting paranoia, and sexual ideation. These observations indicate that fenfluramine is a hallucinogenic agent with a pharmacologic profile in man that is not amphetaminelike.

522. Jasinski, D.R., Griffith, J.D., and Carr, C.B.: Etorphine in man. I. Subjective effects and suppression of morphine abstinence. *Clinical Pharmacology and Therapeutics* 17:267–272 (1975).

The effects of etorphine, a potent morphinelike drug, were qualitatively and quantitatively compared to those of morphine. In nondependent subjects, etorphine in doses of 0.025, 0.050, and 0.100 mg produced pupillary constriction and morphinelike subjective effects and euphoria. Etorphine was 500 times as potent as morphine, with a very rapid onset and short duration of action. In morphine-dependent subjects, etorphine suppressed abstinence but for a shorter period than morphine. These studies indicate that in man etorphine is a morphinelike drug with a high abuse potential.

523. Jasinski, D.R., Griffith, J.D., Pevnick, J.S., and Clark, S.C.: Progress report on studies from the Clinical Pharmacology Section of the Addiction Research Center. *Committee on Problems of Drug Dependence.* Washington, D.C.: National Academy of Sciences, National Research Council, 1975.

Oral *d*-propoxyphene napsylate (PN) and oral *d*-propoxyphene

hydrochloride (PH) produced typical morphinelike subjective effects, miosis, and suppression of abstinence. PH was 1/30th to 1/40th less potent than subcutaneous morphine. PN was 1.5 to 2.5 times less potent than PH with a slower onset than PH. PN was successfully substituted for a 19-day period in two subjects dependent upon morphine. Azidomorphine is a typical morphinelike agent in man. Butorphanol produces subjective effects which are more similar to nalorphine than morphine and does not clearly suppress or precipitate abstinence in morphine-dependent subjects. Benzphetamine produces typical amphetaminelike subjective and physiologic effects in man. Fenfluramine and chlorphentermine, on the other hand, produce effects which are not amphetaminelike.

524. Jones, B.E. and Prada, J.A.: Drug-seeking behavior during methadone maintenance. *Psychopharmacologia* 41:7–10 (1975).

Six subjects were given the opportunity to work for saline placebo and hydromorphone (4 mg i.v.) several times weekly before and during a period of maintenance on methadone (100 mg p.o. daily). Measures of pupillary change and reports of "liking" in response to hydromorphone dropped to saline control levels when the daily dose of methadone was approximately 60 mg. Half of the subjects continued to work intermittently for hydromorphone for 4 weeks while they were receiving 100 mg of methadone daily. These data support the assumption that methadone maintenance reduces the reinforcement value of other opiates and behaviors associated with obtaining them.

525. Kay, D.C.: Human sleep during chronic morphine intoxication. *Psychopharmacologia* 44:117–124 (1975).

The sleep of six opiate addicts was studied for 11 nights during three phases of a chronic morphine cycle. The control phase consisted of 5 consecutive nights before morphine administration. The induction phase consisted of 1 night at 21–36 days after the onset of morphine administration, when the daily dose was 140–220 mg. The stable dose phase consisted of 5 consecutive nights after the subjects had received 240 mg of morphine daily for 8–19 weeks. No sleep could be studied during the withdrawal phase. Sleep was continuously monitored with EEG, EMG, and EOG. Chronic morphine produces signs of a small but persistent sleep disturbance: delta sleep (early night) becomes less stable and shifts toward later in the night, waking state increases during the middle of the night, REM sleep (especially its activated EEG without eye movements) decreases, the REMS cycle increases, and bursts of delta activity (with mean duration of 5–6 s) increase. Although this disturbance persists throughout the night, it is much less than that seen after single doses of morphine in a previous study. With chronic morphine,

therefore, partial tolerance develops to the sleep disturbance produced by morphine. The small but persistent nocturnal arousal during chronic morphine contrasts with the sedation seen during chronic methadone. Both opioids produce an increase in delta bursts during chronic administration, which might be an EEG phenomenon specific to chronic opioid intake.

526. KAY, D.C.: Human sleep and EEG through a cycle of methadone dependence. *Electroencephalography and Clinical Neurophysiology* 38:35–43 (1975).

The effects of oral methadone on EEG and sleep were studied in six male postaddicts. Continuous nocturnal measurement of EEG, EMG, and EOG was used to define sleep patterns. Period analysis and power spectral analysis were performed on each 8-min sample of daytime (eyes closed) EEG. Both sleep and EEG were studied during a predrug control period, during the methadone induction phase (45–60 mg/day), stabilization phase (100 mg/day), and then 6, 10, 13, 18, and 22 weeks after withdrawal. One subject did not complete the last two withdrawal sessions. While on methadone, subjects reported that they slept more and also showed an increase in slow wave activity and a decrease in fast wave activity of their EEG during this time. Nocturnal sleep was not markedly altered during the chronic administration of methadone. Subjects reported an increase in dreaming soon after withdrawal, and then 3–5 weeks of nocturnal insomnia. At the sixth week after withdrawal, slow wave activity in the daytime EEG was decreased, fast wave activity was increased, and mean EEG frequency was increased. REM sleep and delta sleep were increased during withdrawal. These data provide further evidence that chronic administration of narcotic analgesics may induce persistent functional changes in the central nervous system.

527. MARTIN, W.R.: The contributions of Dr. Harris Isbell to drug abuse research. *Committee on Problems of Drug Dependence.* Washington, D.C.: National Academy of Sciences, National Research Council, 1975.

528. MARTIN, W.R.: The pharmacologic treatment of narcotic addiction other than methadone maintenance. *Committee on Problems of Drug Dependence.* Washington, D.C.: National Academy of Sciences, National Research Council, 1975.

529. MARTIN, W.R.: Regulation, abuse and diversion potential of Papaver bracteatum. American Medical Association Symposium on Supplies of Opium for Medical Use (1975).

530. MARTIN, W.R.: Treatment of heroin dependence with nal-

trexone. In: Masserman, J.H. (ed.): *Current Psychiatric Therapies.* pp. 157–161. New York: Grune & Stratton, 1975.

The long duration of action and oral effectiveness of cyclazocine and naltrexone made them potentially useful drugs in the treatment of narcotic addiction. The fact that naltrexone is two to three times more potent than naloxone, is a pure narcotic antagonist that is effective orally and that has a long duration of action, and does not appear to be toxic makes it an especially useful drug for the treatment of the highly motivated addict. Naltrexone blocks the euphorigenic effects of narcotics and prevents the development of physical dependence to them thus providing a circumstance whereby conditioned abstinence and conditioned drug-seeking behavior can be psychologically extinguished and protracted abstinence physiologically extinguished. Since narcotic antagonists will precipitate abstinence in the narcotic addict it is first necessary to withdraw them. The presence of physical dependence can frequently be diagnosed by the administration of a small test dose of naltrexone. If the patient is not physically dependent he may then be stabilized on 50 mg of naltrexone a day which will provide an adequate level of protection for over 24 hours.

531. Martin, W.R., Gilbert, P.E., Eades, C.G., Thompson, J.A., and Huppler, R.: Progress report on the animal assessment program of the Addiction Research Center. *Committee on Problems of Drug Dependence.* Washington, D.C.: National Academy of Sciences, National Research Council, 1975.

532. Martin, W.R., Sloan, J.W., Buchwald, W.F. and Clements, T.H.: Neurochemical evidence for tryptaminergic ascending and descending pathways in the spinal cord of the dog. *Psychopharmacologia* 43:131–134 (1975).

The brain and spinal cord of the chronic spinal dog contained higher levels of tryptamine than comparable regions of the intact dog. The most significant brain elevations were found in the cerebellum and mesencephalon. Further, tryptamine in the white matter of the spinal cord above the level of transection was higher than below. These findings have been interpreted as indicating that there are tryptaminergic pathways descending in the white matter of the spinal cord from the mesencephalon, cerebellum, and rostral spinal cord. The level of tryptamine below the transection was not different from that found in the intact dog, suggesting that there are not only descending but ascending tryptaminergic pathways and that when the axons are transected, tryptamine accumulates proximal to the level of transection.

533. Risner, M.E.: Intravenous self-administration of *d*- and

l-amphetamine by dog. *European Journal of Pharmacology* 32:344–348 (1975).

The relative potency of *d*- and *l*-amphetamine to maintain i.v. self-administration behavior was studied. Five dogs were trained to work for response-contingent drug infusions until a stable drug intake per 4 h daily session was achieved. Then 2-unit doses of *d*-amphetamine (0.05 and 0.10 mg/kg/infusion) and 3-unit doses of *l*-amphetamine (0.20, 0.40 and 0.80 mg/kg/infusion) were evaluated in a parallel line bioassay. Each combination of drug and unit dose was examined separately for five consecutive daily sessions. Order of treatment presentation was determined by a Latin square design. By comparing the unit doses of *d*- and *l*-amphetamine which yielded the same rate of self-administration it was found that 1 mg of the *l*-isomer is equivalent to 0.17 mg of the *d*-isomer.

534. Risner, M.E. and Jones, B.E.: Self-administration of CNS stimulants by dog. *Psychopharmacologia* 43:207–213 (1975).

Drug-naive dogs were trained to respond for intravenous infusions of either *d*-amphetamine, phenmetrazine, or methylphenidate until a stable response rate per 4-h daily session was achieved. The magnitude of reinforcement (i.e., mg/kg/infusion) was then varied systematically across a wide range for each drug. An inverse relationship between unit dose and number of self-administered infusions per session was seen. Thus, total drug intake per session remained relatively constant and was independent of unit dose. Using a parallel line bioassay design, the relative potencies of *d*-amphetamine, phenmetrazine, and methylphenidate to maintain self-administration were estimated. By comparing the unit doses of *d*-amphetamine which yielded the same rate of self-administration it was found that 1 mg of phenmetrazine is equivalent to 0.1 mg of *d*-amphetamine. It was also determined that 1 mg of methylphenidate is equivalent to 0.75 mg of *d*-amphetamine. These data indicate the dog can be used to assess the reinforcing properties of psychomotor stimulants.

535. Sloan, J.W., Martin, W.R., Clements, T.H., Buchwald, W.F., and Bridges, S.R.: Factors influencing brain and tissue levels of tryptamine: Species, drugs and lesions. *Journal of Neurochemistry* 24:523–532 (1975).

With a modification of the spectrophotofluorometric (SPF) method of Hess and Udenfriend (1959) (*J. Pharmac. Exp. Ther.* 127:175–177), brain tryptamine levels in the rat (20.9 ng/g) and guinea pig (20.7 ng/g) were found to be less than those in the dog (32.1 ng/g) and cat (52.2 ng/g). Regional distribution studies in the dog and cat showed that tryptamine was present in all major brain regions with highest concen-

trations in the spinal cord. Blood levels of tryptamine in the guinea pig, dog, and cat (6–7 ng/ml) were lower than brain levels. Pargyline significantly increased brain tryptamine in both the dog and cat; whereas, isocarboxazid (after 4 h) increased brain tryptamine levels in the dog but decreased brain levels in the cat. Reserpine (0.5–1.0 mg/kg per day for 1–4 days) did not significantly decrease brain, spinal cord, or blood tryptamine levels in the dog. Spinal cord transection did not decrease tryptamine levels below the lesion in the chronic spinal dog.

536. Yeh, S.Y. and McQuinn, R.L.: GLC determination of heroin and its metabolites in human urine. *Journal of Pharmaceutical Sciences* 64:1237–1239 (1975).

Heroin and its metabolites, 6-monoacetylmorphine, morphine, and normorphine, were determined in human urine with a GLC procedure. Heroin was extracted with chloroform at pH 4.5 and chromatographed at a temperature programed from 200–250° by 8°/min. 6-Monoacetylmorphine and morphine were extracted with ethylene dichloride containing 30 percent isopropanol at pH 8.5, and normorphine was extracted at pH 10.4 with the same solvent. The extract was derivatized with trimethylsilyl-imidazole and chromatographed at 230° for the determination of 6-monoacetylmorphine and morphine and at 220° for normorphine and morphine.

537. Yeh, S.Y.: Question about the formation of norcodeine from morphine in man. *Journal of Pharmacy and Pharmacology* 27:214–215 (1975).

A paper reporting the isolation and characterization of norcodeine as a morphine metabolite in man by Boerner, Roe, and Becker (1974) has been questioned. Based on the amount of codeine present in the morphine sulfate and the biotransformation of codeine to norcodeine, it is possible that norcodeine identified in the urine by Boerner et al., (1974) could have come from codeine present as a contaminant in the morphine sulfate administered.

538. Yeh, S.Y.: Urinary excretion of morphine and its metabolites in morphine-dependent subjects. *The Journal of Pharmacology and Experimental Therapeutics* 192:201–210 (1975).

Morphine, morphine glucuronide, morphine ethereal sulfate, normorphine, and total normorphine in three consecutive 24-hour urines of four morphine-dependent subjects receiving morphine sulfate 60 mg s.c. q.i.d. have been determined with thin-layer chromatography and gas-liquid chromatography. With thin-layer chromatography the mean daily excretion of free morphine was 10 percent of the administered dose; morphine glucuronide, 65 percent; total (free and acid

hydrolyzable conjugate) morphine 85 percent; and total normorphine, 3.5 percent. With gas-liquid chromatography, the percentage excretion for free morphine was 10 percent; total morphine, 74 percent; free normorphine, 1 percent; and total normorphine, 4 percent. The excretion of total drug was linearly related to the volume of the daily urine output.

AUTHOR/EDITOR INDEX

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