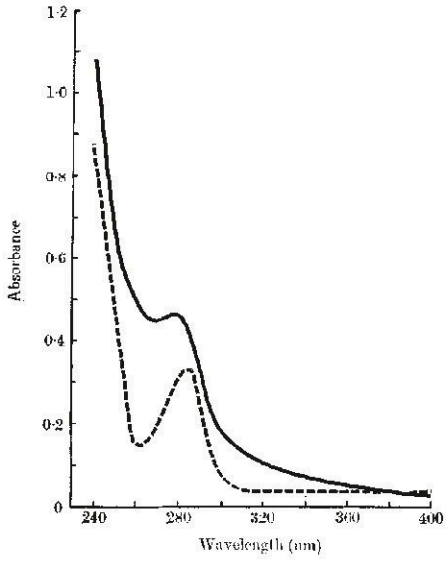

Fig. 2. Ultraviolet absorption spectrum of isolated morphine–glutathione conjugate (———) in aqueous solution and morphine (– – –) in ethanol solution.

paper chromatography sequentially in solvent systems[3] (*sec*-butanol–*tert*-butanol–2-butanone–water, diethylamine (40 : 40 : 80 : 50 : 1) and *sec*-butanol–88 per cent formic acid–water (75 : 15 : 10)) confirmed the presence of glycine, glutamic acid and cystine in the hydrolysate.

These observations furnished strong evidence for conjugation of glutathione with morphine through a covalent C–S bond. N-[*methyl*-^{14}C] codeine and N-[*methyl*-^{14}C] morphine 3-glucuronide in similar conditions gave evidence of formation of 23 and 20 per cent of respective conjugates. N-[*methyl*-^{14}C] morphine oxide in similar conditions without ferrous iron also showed the formation of conjugate (33 per cent). 7,8-^{3}H-dihydromorphine did not give the interaction product in these conditions. Although the exact mechanism of addition of glutathione to morphine is not clear, the probable positions 2, 11 could be ruled out for these would involve the formation of a semiquinone at 3-phenolic group which could not occur in the case of codeine and morphine 3-glucuronide. One possibility is conjugation at C8 with addition of glutathione at the 7,8 double bond by activation of this bond through partial conversion of 6-alcoholic group to a ketone (morphinone) by the redox system of the large excess of glutathione. Addition of thiols to double bonds by free radical mechanism[4–6] and to α,β-unsaturated ketones[7,8] has previously been reported. Attempts to prepare larger quantities of interaction product by condensation of stoichiometric amounts of morphine and glutathione have not been successful.

Reactions of glutathione with adrenaline[9], adrenochrome[10], oestrone and oestradiol[11,12] to give peptide conjugates have recently been reported and it has been postulated that these may have a carrier-type action and may regenerate the original compound at appropriate *p*H. The high concentration of this tripeptide in rat liver[13] and presence of a rat liver enzyme catalysing conjugation with glutathione of a wide variety of compounds have also been described[14]. Minor conjugation of morphine with some ninhydrin-positive material *in vivo* in the dog has recently been reported[15]. Synthesis of protein and RNA are apparently required in the central nervous system for development of tolerance to narcotic drugs in experimental animals and agents like actinomycin D block the development of such tolerance[16]. Evidence has recently been presented[17] that a water-soluble dialysable small peptide or protein extracted from the brain of tolerant rats or dogs could confer tolerance to analgesic effects of morphine when injected into mice. Further, studies[18] on distribution of N-[*methyl*-^{14}C] morphine in the central nervous system of nontolerant and tolerant dogs have shown that higher levels of "conjugated" morphine were usually found in temporal cortex (white and grey) of tolerant compared with nontolerant dogs, and levels of free morphine were much lower in tolerant dogs after 4 h compared with nontolerant, and this "conjugated" morphine could not be demonstrated in the temporal cortex of animals treated with nalorphine. Studies[19] on the intracellular distribution and tissue binding of 7,8-[^{3}H] dihydromorphine in the rat which were similar to those reported[20] for N-[*methyl*-^{14}C] levorphanol have shown that brain nuclear fraction associated with nuclei and cell membranes consistently contained 10–20 per cent of radioactivity of homogenate, implying association of a portion of this drug with cell membranes. The interaction of morphine and glutathione in such mild conditions is interesting because, if this were to occur in brain, not only might protein structure be altered but reaction with SH enzymes and change in cellular thiol groups might interfere with metabolic processes; and this might bear on development of tolerance to morphine-like analgesics.

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Marijuana and the Use of Other Drugs

It is well established that the use of marijuana by young people is positively correlated with at least the experimental use of other drugs[1]. The probability that an individual uses the strong hallucinogens such as LSD and other drugs rises sharply with increasing frequency of marijuana use[2]. Such associations are not, of course, sufficient to establish causal relationships between the use of one drug and another. It seems quite likely that important sociological factors contribute to the progression from marijuana to more hazardous drugs. Goode has found that frequent marijuana users tend to limit their social life to persons in the illicit drug subculture and thus frequently have the opportunity of trying

other drugs[2]. Chronic marijuana intoxication may also contribute to the generally poor reality orientation manifested by many adolescent drug users. This, in turn, can lead to poor judgment concerning the use of the more dangerous drugs. On the other hand, it has been found that older users of marijuana, introduced to the drug about 20 years ago, contain a much higher than average proportion of heavy alcohol users, which suggests that personality and other pre-existing variables are also related to the use of multiple intoxicants[3].

An unexplored aspect of the interaction between the use of marijuana and other drugs is the effect of suppressing the marijuana market. A shortage of marijuana was reported during the summers of 1968 and 1969. The United States administration sought further to diminish the supply by means of Operation Intercept during the autumn of 1969[4]. Some of the rumoured effects of the shortages were higher prices, the sale of poor grade marijuana grown in the United States and an increase in the use of other drugs as substitutes for marijuana. We have investigated the effects of these shortages during the summer of 1969.

In October 1969, during Operation Intercept, we surveyed 478 students from a university in Los Angeles, and 116 patients from the Los Angeles Free Clinic which specializes in treating drug users. The students were members of one graduate and two undergraduate psychology classes. Because we were primarily interested in the interaction between the use of marijuana and other drugs, we included a large (335 members) somewhat unorthodox class in human relations which we thought would contain a fairly high proportion of marijuana users. Thus the results are not representative of the incidence of drug use in the overall campus population. The mean age of the sample was 20·1 yr, and it was 51 per cent male, 91 per cent white, 94 per cent single, and had completed 13·6 mean yr of school.

The patients were people attending the clinic on two successive nights. Their mean age was 20·9 yr, and they were 38 per cent male, 97 per cent white, 86 per cent single, having completed 14·8 mean yr of school. Of these people 51 per cent were in full or part time employment, 28 per cent were unemployed and 21 per cent were students.

Data were collected by means of an anonymous, self-administered questionnaire requiring about 5 to 10 min for completion. Items were designed primarily to reveal the incidence and frequency of use of various drugs; whether those using marijuana had reduced their use during the previous 5 months as a consequence of its unavailability; whether the frequency of use of other drugs had increased as a result of the shortage of marijuana. We also compared the prices paid for marijuana during the spring, summer and autumn of 1969.

Students completed their questionnaires during a class and the response was virtually 100 per cent. The study was simply described as a survey of patterns of drug use being conducted as a graduate student project. In the Free Clinic questionnaires were passed out in the waiting room with the approval of the administrators. Virtually everybody attending agreed to complete the form.

As with other surveys of this type, the validity of the results depends on the cooperation of the respondents. It might be argued that some answers would be biased so as to reflect unfavourably on the current drug laws, and our only safeguards against this were the usual pleas that the validity of the study depended on the accuracy of the answers, plus the fact that it was a student project rather than one conducted by the school administration. In addition, there is the advantage of a virtually 100 per cent response. (The difficulty of obtaining accurate self-report information on drug use has probably been overemphasized—most investigators find that people are remarkably candid in providing such data.)

Table 1 shows the percentage of students and patients who have used various drugs, and the current frequency of marijuana use. The incidence of use among the ninety-seven members of the second undergraduate class in introductory psychology was much lower than in the large, atypical class (for example, LSD or other strong hallucinogen, 10 per cent; and opiates or cocaine, 0 per cent). It is interesting that fewer students than patients used tobacco and alcohol.

Table 1. INCIDENCE OF DRUG USE FOR STUDENT AND FREE CLINIC SAMPLES

Drug	Students		Free clinic	
	Male (N=245) Per cent	Female (N=233) Per cent	Male (N=44) Per cent	Female (N=72) Per cent
Tobacco (current)	29	21	68	57
Alcohol (>2 drinks/day)	6	1	24	9
History of heavy alcohol use*	20	5	43	31
Marijuana (1 or more times)	73	49	95	89
Daily	3	0	32	26
3–6 times/week	11	5	25	24
1–3 times/month	30	20	23	22
<1 time/month	29	23	16	17
Hashish (1 or more times)	53	35	90	89
Any non-medical use of:				
Sedatives	16	15	57	60
Stimulants	32	21	80	67
LSD	24	8	82	69
⩾5 times	13	1	54	48
Other strong hallucinogens	30	16	79	74
Opium, morphine or cocaine	14	3	65	41
⩾5 times	3	1	40	20
Heroin	3	0	37	24
⩾5 times	1	0	18	11
Methamphetamine (injected)	3	0	20	29

* Heavy alcohol use defined as five or more drinks during 3–4 h, two or more times per week for a minimum of 1 year.

Table 2. DRUG USING BEHAVIOUR AS A FUNCTION OF FREQUENCY OF MARIJUANA USE: STUDENT SAMPLE

Behaviour / Drug use	Marijuana use by males			Marijuana use by females		
	0–10 times (N=122) Per cent	>10 times <1×/wk (N=61) Per cent	>10 times ⩾1×/wk (N=62) Per cent	0–10 times (N=161) Per cent	>10 times <1×/wk (N=44) Per cent	>10 times ⩾1×/wk (N=28) Per cent
Tobacco (current)	16	34	50	13	43	32
Alcohol (>2 drinks/day)	2	2	16	0	2	4
History of heavy alcohol use	13	20	34	3	5	11
LSD	2	17	72	0	17	39
Opium, morphine or cocaine	2	12	41	0	7	19
Heroin	1	2	10	0	0	0
Marijuana*						
Has had own supply	—	39	85	—	25	50
Prefers hashish to marijuana†	—	39	48	—	32	32
Experienced marijuana shortage	—	38	53	—	34	54
Substituted other drugs (inc. alc.)	—	33	44	—	11	46

* These questions were only asked of those who had used marijuana more than ten times.
† Percentage of those having experience with both hashish and marijuana.

Table 3. DRUG USING BEHAVIOUR AS A FUNCTION OF FREQUENCY OF MARIJUANA USE: FREE CLINIC SAMPLE

Behaviour / Drug use	Marijuana use by males		Marijuana use by females	
	⩽2×/wk* (N=12) Per cent	⩾3×/wk (N=25) Per cent	⩽2×/wk* (N=28) Per cent	⩾3×/wk (N=36) Per cent
Tobacco (current)	58	72	57	61
Alcohol (>2 drinks/day)	50	12	14	6
History of heavy alcohol use	50	48	32	33
LSD	75	96	67	83
Opium, morphine or cocaine	30	90	43	51
Heroin	0	54	33	24
Marijuana				
Has had own supply	50	87	50	81
Prefers hashish to marijuana	60	57	43	64
Experienced marijuana shortage	50	72	35	47
Substituted other drugs (including alcohol)	42	64	17	44

* Does not include respondents who reported using marijuana less than ten times.

Tables 2 and 3 show the incidence of other drug use as a function of frequency of marijuana use for the two samples. It was necessary to group the data differently for the student and Free Clinic samples because of the much higher frequency of marijuana use in the latter. The use of other drugs is strongly correlated with the

frequency of marijuana use in the student group, and to a lesser extent in the sample of patients. For the latter group, there is a reversal in terms of alcohol use—frequent marijuana users report less use of alcohol; subsample sizes are relatively small, however.

Tables 2 and 3 also detail other behaviour related to marijuana use for people using it ten or more times. The information about supply gives the percentage of respondents who sometimes, or generally, have their own supply rather than depending on marijuana provided by others. The preference for hashish over marijuana is more common among patients than students. Of those using marijuana ten or more times, 44 per cent of the students and 51 per cent of patients reported that their frequency of marijuana use was below normal at some time between May and October 1969, as a consequence of the unavailability of marijuana. Of those reporting a shortage of marijuana, 76 per cent of students and 84 per cent of patients reported that they increased their consumption of one or more other drugs (including alcohol) because of the unavailability of marijuana.

Table 4. PERCENTAGE OF RESPONDENTS EXPERIENCING MARIJUANA SHORTAGE WHO SUBSTITUTED OTHER DRUGS

Drug	Students		Free clinic	
	Male (N=56)	Female (N=30)	Male (N=24)	Female (N=25)
Hashish	52	37	54	44
Alcohol	55	23	50	48
Sedatives	9	10	29	24
Stimulants	11	7	21	16
LSD	16	7	50	48
Other strong hallucinogens	23	13	37	28
Opiates or cocaine	2	3	25	24

Table 4 shows the drugs which were substituted. For the students, an increase in the consumption of other drugs was largely limited to hashish, alcohol and the strong hallucinogens. The patients had a similar preference, but a significant number also reported substituting sedatives, stimulants and opiates.

During the spring of 1969 the mean cost of marijuana per ounce reported by the respondents was $10.13. In October 1969, the mean reported price was $11.87 per ounce– an increase of 17 per cent.

In countries where cannabis (marijuana) has been regulated by the Government, its relative popularity with respect to alcohol has been manipulated by varying the respective taxes[5]. Similarly, suppression of opium availability in India resulted in increased use of cannabis[6]. It is not surprising that reduced availability of marijuana in the United States results in the substitution of both licit (alcohol) and illicit intoxicants. The current marijuana epidemic is too new, and too much in a state of flux, to permit an assessment of the net consequences of reducing its availability solely in terms of the substitution of other drugs. The effective suppression of marijuana might well decrease the number of adolescents who start to use illicit drugs. On the other hand, the results of our survey indicate that there is a need to consider how social policies directed at controlling one drug affect behaviour with respect to competing intoxicants.

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New Rodenticide, 'MR-100', containing a Taste Enhancer

IT has usually been assumed that the more acceptable a rodenticide is, the more effective it will be in the field control of rats, but this has not been verified experimentally: we now report data supporting this supposition. The most effective rodenticides for domestic and agricultural use are the anticoagulants, and grain has hitherto been the most suitable carrier[1].

A new material 'Dexide', developed by Monsanto, seems to be particularly acceptable to white rats, *R. rattus*, and *R. norvegicus*, probably because it enhances the taste of the carrier grain. In a programme of tests to evaluate this compound, we considered variables such as the types of grain, grain size, ratio of components, moisture level, methods of formulations, preservatives, physical form, and alternative taste enhancers. We measured acceptability in terms of comparative consumption in cage tests, first with white rats and, then, for confirmation, with *R. norvegicus*, *R. rattus* and *Mus musculus*. On the basis of our results, we have formulated a new rodenticide, 'MR-100', containing 3-(α-phenyl-β-acetylethyl)-4-hydroxycoumarin ('Warfarin') (0·025 per cent), 'Dexide' and N′-2-quinoxalylsulphanilamide (sulphaquinoxaline) (0·025 per cent). 'Dexide' is a carbohydrate with flavour material. The rate of consumption of this material was enhanced six to one compared with conventional grain-based, anticoagulant rodenticides.

We report here comparative studies which include evaluations of other rodenticides referred to as 'A' and 'B'. Rodenticide 'A' is a grain-based material containing 'Warfarin' (0·025 per cent) and 'B' is a pelletized, grain-based material also containing 'Warfarin' (0·025 per cent). Each compound was assessed in three cage tests, two of which were run simultaneously and the third two months later. We used nine wild rats (*R. norvegicus*), individually caged and given water *ad libitum* and a choice of 'MR-100', commercial rodenticide, and fresh ground grains (61 per cent corn meal and 39 per cent ground oats).

Table 1. CAGE TEST COMPARISON OF 'MR-100' WITH FRESH GRAINS AND OTHER RODENTICIDES

	Percentage of total consumption			Preference ratio	
	'MR-100'	Grains	Rodenticide "A"	'MR-100'/ grains	'MR-100'/ rodenticide "A"
Total population	66·5	22·6	10·8	3·0 : 1	6·2 : 1
Female	59·6	26·8	13·6	2·2 : 1	4·4 : 1
Male	72·8	18·9	8·3	3·8 : 1	8·7 : 1
			"B"		"B"
Total population	62·1	34·5	3·3	1·8 : 1	19 : 1
Female	49·0	46·2	4·7	1·1 : 1	10 : 1
Male	75·5	22·6	1·9	3·3 : 1	40 : 1

No significant difference between the results of the three tests was detected; the average consumptions for the total population of male and female rats are given in Table 1. All rats preferred 'MR-100' to either rodenticide or to fresh grains, although the preference was more enhanced in males. Because rodenticide 'B' proved to have the poorest acceptability in these tests, 'A' was selected for the field tests. Although tests had shown that 'MR 100', which contains stabilizing additives, maintains its effectiveness over time, to compensate for