in these animal hosts a significant number of schistosomes escaped destruction. Six to 12 months were required until production of viable eggs was resumed. Therefore, it can be expected that live eggs are absent from the stools of human subjects for a similar period (*4*, *5*), regardless of whether or not all the parasites have been eliminated.

It appears unlikely that the development of hycanthone-resistant schistosomes can be accounted for by the presence of two preexistent populations of worms, one drug-susceptible and one drug-resistant. Such a hypothesis is not consistent with the hepatic shift and other changes involving *all* the worms after the initial treatment. In addition, many months are required for functional and morphological recovery. By contrast, the progeny of these worms proved completely unaffected by this drug. Conceivably a preexistent resistant population might be affected by the products of the dying susceptible schistosomes rather than by the drug itself. This appears unlikely because, when mice were infected with a mixture of cercariae of a susceptible strain and a resistant strain, only a proportion of worms equal to that of the susceptible strain was affected by administration of hycanthone.

Possibly, hycanthone-resistant oocytes are induced or selected by this drug. Since hycanthone has been found to be a potent mutagen (*13*), administration of this compound might contribute to an increase in the drug-resistant oocyte population.

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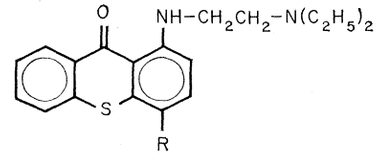
Hycanthone: A Frameshift Mutagen

Abstract. *Rapid spot-test screening of antischistosomal agents reveals that hycanthone is a potent frameshift mutagen while the closely related compound, miracil D, is nonmutagenic in* Salmonella. *Both hycanthone and miracil D are frameshift mutagens for T4 bacteriophage during growth in* Escherichia coli.

Over 1000 mutations in the histidine operon of *Salmonella* have been classified as to type (missense or nonsense base substitution, frameshift, extended deletion) on the basis of reversion analyses and other genetic and biochemical tests (*1*). From among the spontaneously revertible strains we have selected 13 mutants which appear suitable for use in rapid spot-test screening of new compounds for mutagenic activity (Table 1). Each strain produces a low number (about one to ten) non-histidine-requiring colonies when approximately 2×10^8 bacteria are spread evenly on the surface of a petri dish containing enriched minimal medium (*2*). At the plating density utilized, the enrichment in this medium allows most amino acid–requiring mutants to undergo roughly four cell divisions before growth ceases (*3*). Thus we have chosen strains that mutate spontaneously but do so at low frequencies (less than 10^{-8}). The strains also have been chosen for their diversified, yet clear-cut, responses to mutagens in spot tests [see (*4*) and (*5*) for descriptions of spot tests]. Different sensitive tester strains have been described earlier by Ames (*6*). The plating medium allows ready discernment of revertant colonies on an accumulated background population of mutant bacteria exceeding 10^9 per plate. On experimental plates the medium also allows detection of mutations that are delayed in expression and mutations that are induced only in growing bacteria during DNA replication. Further points on methodology and the usefulness and validity of tests of this type are discussed by Ames (*6*).

Conversations with Rogers and Bueding concerning some of their data (*7*) led us to screen by the spot-test procedures a series of compounds potentially useful in the treatment of schistosomiasis. Among these are HC (hycanthone monomethanesulfonate and hycanthone furoate) and MD (miracil D; also known as lucanthone); HC and MD are closely related compounds (*8*) with planar ring structures (Fig. 1) which may allow intercalation into DNA [see (*9*)]. Both hycanthone derivatives behaved similarly in our mutation tests and are therefore both identified as HC although they were tested individually; the furoate is less toxic to bacteria than is the monomethanesulfonate.

In initial tests, crystals of the compounds were applied with sterile toothpicks near one edge of the petri dish; later, tests were performed with the relevant compounds dissolved in distilled water at 10 mg/ml. All manipulations were performed under subdued light and all incubations were carried out in the dark to avoid any possible photodynamic effects. Table 1 shows that HC is effective in eliciting reversions of several frameshift mutations but is inactive in reverting mutations involving base substitutions. Figure 2 shows a test with *hisA3043*. Miracil D is inactive as a mutagen in our tests with *Salmonella*. Tests on additional representative frameshift mutants show



R = –CH_2OH (Hycanthone) or –CH_3 (Miracil D)

Fig. 1. Structures of hycanthone and of miracil D.

Table 1. *Salmonella* histidine-requiring tester strains with varied reversion patterns. Symbols and abbreviations: +, reversions induced by mutagen; 0, no reversions detected in response to mutagen; ICR191, 2-chloro-6-methoxy-9-[3-(2-chloroethyl)aminopropylamino] acridine dihydrochloride; ICR364OH, 2-chloro-6-methoxy-9-[2-(2-hydroxyethyl)aminoethylamino]-1-azaacridine dihydrochloride; HC (hycanthone), 1-[[2-(diethylamino)ethyl]amino]-4-(hydroxymethyl)-thioxanthen-9-one, monomethanesulfonate or furoate; MD (miracil D), 1-[[2-(diethylamino)-ethyl]amino]-4-methylthioxanthen-9-one, monomethanesulfonate; NQ, 4-nitroquinoline-1-oxide; NG, *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine; DES, diethylsulfate; βPL, β-propiolactone; 2AP, 2-aminopurine; UV, ultraviolet irradiation; and SM, phenotypic reversal with streptomycin.

Mutation	Type	Reversion pattern										SM	Origin
		Spontaneous	ICR-191	ICR-364OH	HC	MD	NQ	NG	DES	βPL	2AP	UV		
hisC1743	Nonsense (amber)	+	0	0	0	0	0	+	+	+	+	+	+	NG
hisD1768	Missense	+	0	0	0	0	0	+	+	+	+	+	+	NG
hisC434	Nonsense (amber)	+	0	0	0	0	0	+	+	+	+	+	+	2AP
hisC342	Nonsense (ochre)	+	0	+	0	0	0	+	+	+	+	+	+	2AP
hisC354	Nonsense (ochre)	+	0	0	0	0	0	+	+	0	+	0	0	2AP
hisC163	Missense	+	0	0	0	0	0	+	+	+	0	+	0	Spontaneous
hisC890	Missense	+	0	0	0	0	0	+	+	0	+	0	0	2AP
hisC120	Missense	+	0	0	0	0	0	+	+	0	0	+	0	Spontaneous
hisA3043	Frameshift	+	+	+	+	0	+	+	0	0	0	+	0	ICR191
hisD3052	Frameshift	+	+	+	+	0	+	+	+	0	0	+	0	ICR364OH
hisC3070	Frameshift	+	+	+	0	0	0	0	0	0	0	+	0	ICR364OH
hisD3008	Frameshift	+	0	0	0	0	0	0	0	0	0	+	0	ICR191
hisG3025	Frameshift	+	0	0	0	0	0	0	0	0	0	0	0	ICR191

that HC causes reversion of *his-3002, -3011, -3013, -3031, -3054,* and *-3076* while MD is inactive. Each of these mutants reverts with the acridine half-mustard ICR191, and three also are reverted with nitrosoguanidine (*10*). Frameshift mutants that fail to revert with ICR191 do not respond to HC. Hycanthone does not elicit mutations merely by interfering with the *Salmonella* DNA-repair system since a strain containing a deletion of the *uvrB* locus [strain TA1700 = *his-3076 chl*^{r} *bio*$^-$ *uvrB* (*6*)] responds to HC as well as does the parental strain, *his-3076*.

Hycanthone increases reversion frequencies of two ICR-revertible frameshift mutations in the *rII* region of T4 phage (*11*) when present during phage growth in *Escherichia coli* K-12; MD also serves as a mutagen in this test system (Table 2).

We conclude that HC is a potent mutagen in bacterial systems and engenders frameshifts rather than base substitutions. In most reversion tests, ICR191 is more potent a mutagen than is ICR364-OH (*5, 10*) and HC and 4-nitroquinoline-1-oxide are slightly less potent. Each compound, however, shows a degree of specificity for particular polynucleotide tracts [compare (*10*) and (*12*)]. In *Salmonella* nitrosoguanidine predominantly causes base substitutions (*1, 13*) as well as a low frequency of frameshifts, presumedly a specific subclass of the frameshifts elicited by the other mutagens just discussed (*10, 14*).

The conversion of MD to HC by hydroxylation (Fig. 1) takes place in

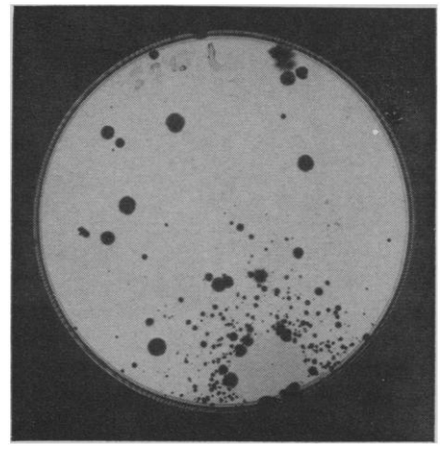


Fig. 2. Photograph of a spot test demonstrating mutagenicity of hycanthone. Approximately 2×10^8 histidine-requiring bacteria (*hisA3043*) were spread on minimal salts medium (*2*) supplemented with 1.25 percent (by volume) liquid Difco nutrient broth. A solution containing approximately 0.2 mg of hycanthone was spotted near the edge of the petri dish. Residual background growth of bacteria is inhibited at the position of drug application. Revertant mutant colonies surround the inhibition zone where hycanthone has diffused into the medium. Distal portions of the plate and additional drug-free plates (not shown) served as controls for spontaneous mutations.

Table 2. Reversion frequencies of T4 *rII* frameshift mutants. Compounds were added 5 minutes prior to phage infection (multiplicity = 3) in M9 salts medium. Infected cells were incubated for 30 minutes, diluted 50-fold in the same medium, and maturation was allowed to proceed for an additional 60 minutes before plating on appropriate hosts to determine total viable phage (burst size, 225 to 250 for untreated) and total revertant phage yields (*11*). Incubations were at 30°C. Compounds were added at the following final concentrations (in micrograms per milliliter): proflavine, 10; NG and ICR191, 20; MD, 30; HC furoate and HC monomethanesulfonate, 100. For abbreviations see legend to Table 1.

Compound added	Percent normal phage yield	Revertants	
		× 10^{-6} viable progeny phage	Ratio of treated to untreated
	Mutant 8-10-64 (proflavine-induced)		
None (spontaneous)	≡100	0.46	
NG	100	0.28	0.6
MD	<1	1.8	3.9
HC furoate	92	1.5	3.3
HC monomethanesulfonate	19	2.0	4.4
ICR191	90	0.54	1.2
Proflavine	90	2.6	5.7
	Mutant 50-62 (ICR191-induced)		
None (spontaneous)	≡100	0.6	
NG	90	0.4	0.7
MD	46	8.0	13.3
HC furoate	92	6.0	10.0
HC monomethanesulfonate	21	11.0	18.3
ICR191	90	23.0	38.3
Proflavine	65	22.0	36.7

Aspergillus and also in the mammal where it is effected by liver microsomes (*8*). Therefore, a test for bacterial mutagenicity of MD in an animal host (*15*) might reveal positive results in contrast to our negative observations on *Salmonella*. We do not know whether the mutagenicity of MD in the T4 test system, in contrast to the *Salmonella* test system, is due to direct activity, to metabolic conversion, or to altered permeability of infected cells. Miracil D is a weak mutagen in *Drosophila* (*16*) and causes achromatic lesions and chromatid breaks in human leukocyte chromosomes in vitro (*17*).

The high degree of mutagenicity of HC and MD in our microbial test systems and other effects of HC (*7*) lead us to view with alarm the widespread clinical testing of these compounds in humans. Most compounds known to be strongly mutagenic for bacteria are either untested or positively indicated as carcinogenic (*6*).

There is no correlation between mutagenic activity in tests with *Salmonella* and antischistosomal activity. The following agents were found to be inactive in spot tests for mutagenicity with the mutants listed in Table 1: potassium antimony tartrate; a nitrothiazole—niridazole [see (*18*)]; four differently substituted tetrahydroquinolines—UK3883 and UK4271 and their 7-chloro- analogs (*19*); a nitrovinylfuran (SQ18,506) and its *N*-acetyl derivative (SQ19,104) (*20*).

While some studies have been performed on the interaction of MD with DNA and its effects on bacterial metabolism (*21*), we know of no comparable analysis of the action of HC.

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Students Reveal Negative Attitudes toward Technology

The juxtaposition of the articles "Taming technology" by Branscomb and "Activist youth of the 1960's" by Horn and Knott (12 March) prompts us to summarize some preliminary findings of a study of student attitudes toward science and technology (*1*). As proposed, the study was intended to examine the factors "affecting not only choice of education and career, but also attitudes towards both science and society." Due to lack of funding, only a preliminary study was carried out.

In the development of the measuring instruments, tests were given to 79 urban students (33 male, 46 female) and 161 rural students (85 male, 76 female) in senior high school. They are a very small sample from a large population, but the results are so far from what one might suspect as to be very disquieting.

A semantic-differential technique (*2*) was used in an attempt to measure attitudes rather than opinions. It is believed that the purpose of the test was not obvious to the population tested. The sample group was not interviewed prior to the test, nor were conventional questionnaires used. Two forms of the test were used for the rural students. The correlation between these forms was $r = 0.97$, indicating a high level of reliability.

It was found that, relative to their self-image, students viewed "man" as cruel, harmful, hard, old, bad, frightening, false, and dishonest. They viewed "scientist" as helpful, wise, and important, but, hard, old, frightening, colourless, and "theirs." The concept "industrialist" was seen most unfavorably—cruel, masculine, hard, foolish, old, bad, frightening, colourless, and dishonest. "Industrialist" was also totally rejected on the mine-theirs scale. Among the 25 percent of urban students that had negative attitudes toward "technology," the ratio of boys to girls was found to be 3 : 1.

What is disturbing is the specter of student activists trying to control the ogre "technology" from a basis of ignorance. We infer from Horn and Knott that activists are essentially "normal" and that they may be reflecting the policies of society at large. If this is so, then the "swing away from science," coupled with the activist ethic, may forecast a serious breakdown in the technological underpinnings of our society.

Surely we must change, but let the change be from an awareness that the facts of existence, which are the subject matter of science, and the facts of consensus, which form our societal structures, are not the same (*3*). A fact of existence is there, implacable and impassable. A fact by consensus is created or modified by agreement, like the spelling of the word "colour."

Much of the revolt against technology is rooted in a confusion between these kinds of facts. The scientist is considered stubborn, the engineer inhuman, because they are unwilling to submit their facts to arbitration. We