Muller (*18*), in a brilliant treatment of the mutation problem in man, has emphasized the relative frequency with which this phenomenon occurs, a point of view with which we are in complete agreement. Our own figure for total mutation rate is somewhat higher than that arrived at by Muller (0.1–0.5), the chief basis for the difference being the more conservative estimate of gene number (5,000–20,000) which he adopted. He has stated that it is unlikely that the total mutation rate in man exceeds 1.0, because, if we assume an approximate equilibrium between the origin of new traits through mutation and their removal through selection, this implies an average of one "genetic death" per individual; it seems to him unlikely that the species could "tolerate" more than this. This concept of "genetic death" is, however, a statistical abstraction that can be misleading. All of us fall far short of the theoretically perfect representative of the species. The various members of a species can each carry a considerable handicap as long as the species as a whole is capable of successfully resisting efforts to dislodge it from its particular ecological niche by other (genetically handicapped) species. Man with his highly developed nervous system and social organization may have developed mechanisms for compensating for theoretical genetic death, mechanisms not operative in lower forms. In other words, the tolerable limit of genetic inefficiency depends upon both inter- and intraspecific selective pressures. Man may have so far negated the interspecific competitions, and so far mitigated and altered the usual intraspecific competitions, that relatively high mutation rates per generation can be tolerated (and on occasion turned to advantage) as long as the integrity of the organ responsible for his success, the brain, is not threatened. Furthermore, the survival of an individual under competition is as a rule not determined by the presence of single genes but by constellations of genes. Each individual who dies for reasons primarily genetic removes some 40,000 genes from circulation. One "genetically determined" death may therefore effect the disappearance of a number of mutations, particularly if there is any tendency for the distribution of unfavorable genes in a population not to follow a normal frequency curve. For these reasons it would seem premature, until more detailed data are available, to postulate a genetically acceptable upper limit for total mutation frequency.

Further research in this area is a prerequisite to intelligent discussion of the problems of induced mutation, as from therapeutic or diagnostic irradiation, or the peacetime or military applications of atomic energy. The dangers of induced mutation can only be evaluated against the background of knowledge of spontaneous human mutation rates. Furthermore, an evaluation of the genetic problems inherent in the recent alterations in the type of selective factors to which human populations are subject likewise revolves around a recognition of the total frequency of mutation which must in each generation in a state of nature be offset by the selective process.

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Cross Resistance of Streptococci to Five *Streptomyces* Antibiotics[1]

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Microorganisms that have acquired resistance *in vitro* or *in vivo* to one antibiotic have been shown to have a cross resistance to other antibiotics to which they had not previously been exposed. This phenomenon is of evident importance in chemotherapy, and may be of significance in understanding the mechanisms of antibiotic activity.

Pansy *et al.* (*1*) induced resistance to chloromycetin and aureomycin separately in strains of *Escherichia coli* and *Micrococcus pyogenes* var. *aureus*. Each resistant strain showed cross resistance to the other antibiotic as well as to terramycin. Herrell *et al.* (*2*) showed that strains of *E. coli* and *Aerobacter aerogenes* resistant to terramycin were also resistant to aureomycin and chloromycetin, but not to streptomycin. *Streptococcus fecalis* and *M. pyogenes* strains resistant to terramycin were resistant to aureomycin, but not to streptomycin or chloromycetin. In contrast, Waksman (*3*) has reported that both streptomycin-sensitive and streptomycin-resistant strains of different mycobacteria were sensitive to neomycin, and

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TABLE 1

ANTIBIOTIC RESISTANCE INDUCED IN GROUP A STREPTOCOCCI

Strain designation	Type	Fold increase after 47 transfers on				
		Streptomycin	Neomycin	Chloromycetin	Aureomycin	Terramycin
C203MV	3	2000	75	37	67	25
B347	2	2000	250	25	100	250
K43	1	3500	583	60	60	125
283T	6	2500	40	17	50	50
5797	25	100	1000	67	50	50
Richards	3	100	2000	12	50	40
B350	2	3000	250	21	130	60

Karlson *et al.* (*4*) have shown a therapeutic effect of neomycin on experimental tuberculosis in guinea pigs infected with streptomycin-resistant tubercle bacilli. Waksman and co-workers (*5*) found aureomycin effective against both streptomycin-resistant and streptomycin-sensitive strains of *Mycobacterium* 607.

TABLE 2

CROSS RESISTANCE OF STREPTOMYCIN-RESISTANT AND NEOMYCIN-RESISTANT STREPTOCOCCI

Strain designation	Fold increased resistance to *neomycin* after induced streptomycin resistance	Fold increased resistance to *streptomycin* after induced neomycin resistance
C203MV	2	3
B347	0	5
K43	0	4
283T	2	7
5797	2	20
Richards	4	20
B350	0	7

To study possible cross resistances among five of the *Streptomyces* antibiotics, individual resistance to streptomycin, neomycin, chloromycetin, aureomycin, and terramycin was induced in each of seven typable Group A β-hemolytic streptococci by the plate-to-plate method previously described (*6,7*). The strains are designated C203 MV (Type 3), Richards (Type 3), K43 (Type 1),[3] 283T (Type 6),[3] 5797 (Type 25),[3] B347 (Type 2),[3] and B350 (Type 2).[3] The organisms remained both group- and type-specific throughout the period of the experiment.

Table 1 summarizes the fold increase in resistance induced separately in the streptococci to each of the five antibiotics after 47 serial transfers on medium containing one antibiotic. The seven streptococci resistant to one antibiotic were plated in series on media containing each of the four other antibiotics. The cross resistance of streptomycin-resistant organisms to neomycin and of neomycin-resistant strains to streptomycin is given in Table 2. Similarly, aureomycin-resistant streptococci showed an increased resistance to terramycin, and terramycin-resistant ones a moderate degree of resistance to aureomycin. The results are given in Table 3. No other cross resistance was observed. Chloromycetin-resistant organisms were as sensitive as their parent strains to each of the other four *Streptomyces* antibiotics studied.

[3] These organisms were supplied by Stuart Elliott.

TABLE 3

CROSS RESISTANCE OF AUREOMYCIN-RESISTANT AND TERRAMYCIN-RESISTANT STREPTOCOCCI

Strain designation	Fold increased resistance to *terramycin* after induced aureomycin resistance	Fold increased resistance to *aureomycin* after induced terramycin resistance
C203MV	27	9
B347	27	20
K43	13	11
283T	27	13
5797	13	7
Richards	13	5
B350	13	5

These data suggest that aureomycin may not be effective in the control of infections from terramycin-resistant organisms or terramycin in infections from aureomycin-resistant strains. They demonstrate less clearly the cross resistance between neomycin and streptomycin. The maximum of a fourfold increase in resistance to neomycin after induced streptomycin-resistance, although reproducible, may be within the limits of experimental error; the reverse of this with streptomycin-resistance after induced neomycin-resistance is probably a significant rise.

The concept at present widely held, that the use of one antibiotic is not likely to interfere with the subsequent use of another related drug, is made less tenable by these data. This statement must be qualified by the reminder that these results were observed only in β-hemolytic streptococci with resistance induced *in vitro* and may not apply to other organisms or to natural resistance.

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