present experiments the 6-carbon dicarboxylic acids and β-hydroxyisovalerate were poorly utilized, their participation in cholesterol synthesis and their metabolic relation to DMA remain unsettled.[11]

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THE ANTITUBERCULOSIS ACTIVITY OF SOME ETHYLMERCAPTO COMPOUNDS

Sir:

In the course of studies dealing with the phenomenon of nitrification in soil[1] it was noted that proliferation of nitrifying organisms was inhibited by several alkyl mercapto acids. This led to the testing of β-ethylmercaptopropionic acid (I) for antibacterial activity. Only slight activity was found *in vitro* against several gram-positive and gram-negative bacteria. Definite protection was, however, afforded to mice infected with the H37Rv strain of *Mycobacterium tuberculosis* (human type) when fed β-ethylmercaptopropionic acid at a level of 0.2% in diet *ad libitum*. Further tests with other compounds of this type indicated that the ability of a given compound to inhibit proliferation of nitrifying bacteria is not a sufficient qualification for *in vitro* activity in experimental tuberculosis.

A systematic investigation of the relationship of structure to *in vivo* antituberculosis activity in derivatives of I was next undertaken. Substitution of various terminal alkyl groups (methyl through octadecyl) on the sulfur atom gave activity only with the C_2H_5–homolog. Aryl and heterocyclic moieties were equally disappointing. Variation of the distance between sulfur and carboxyl to give mercaptoacetic through mercaptovaleric acids indicated that the β-relationship between sulfur and carboxyl was essential. Replacement of carboxyl by $-CH_2OH$, $-CHO$, $-COOR$ was achieved with retention of activity. Elevating the oxidation state of sulfur to sulfoxide or sulfone destroyed the capacity to inhibit the experimental tuberculosis. Replacement of the sulfur atom in I by oxygen or nitrogen was also deleterious. In an effort to find compounds with more acceptable properties, S-ethyl-L-cysteine (II) was early tested and shown to be worthy of practical consideration on the basis of efficacy and acute and chronic toxicity studies.

Concurrently with the study of the structure requirements for efficacy in I, attention was given to the possible metabolic fate of β-ethylmercaptopropionic acid in the animal body. This seemed especially pertinent in view of the lack of *in vitro* activity. With the testing of ethyl disulfide a significant increase in efficacy over I was noted.

Results of the above tests opened a broad horizon for the study of C_2H_5–S–R compounds. In general, structural modifications which decreased the tendency for cleavage of the C_2H_5S-linkage decreased the antituberculosis activity. Of the more than three hundred and fifty samples examined to date, over fifty have shown effectiveness at or below 0.2% in diet.

During the course of our studies with C_2H_5–S–R compounds we encountered the report by Del Pianto[2] on the antituberculosis effect noted after injecting a combination of sodium ethyl thiosulfate and mercaptobenzothiazole derivatives in guinea pigs. In our hands sodium ethyl thiosulfate alone was more active orally than by subcutaneous injection in mice.

Table I is intended to show the relative activities of representative members of some of the classes of compounds covered in this investigation. On the basis of data obtained by direct comparisons in mice, it may be said that S-ethylcysteine (L and DL) is at least twice as active as pyrazinamide and several times more effective than *p*-aminosalicylic acid.[3] Compound II was equally effective against isonicotinic acid hydrazide resistant and sensitive strains of *Mycobacteria*.

TABLE I

ANTITUBERCULOSIS ACTIVITY OF SOME C_2H_5–S–R COMPOUNDS

		Antituberculosis activity
I	C_2H_5-S-CH_2CH_2COOH	+
II	C_2H_5-S-$CH_2CH(NH_2)COOH$ (L and DL)	+
III	C_2H_5-S-$CH_2CH(NH_2)COOH$ (↓ O)	−
IV	C_2H_5-S-S-C_2H_5	++
V	C_2H_5-S-S-C_6H_5	+
VI	C_6H_5-S-S-C_6H_5	−
VII	C_2H_5SH	++
VIII	C_2H_5-S-CO-O-C_2H_5	++
IX	C_6H_5CO-S-C_2H_5	++
X	$C_6H_5C(=NH)$-S-C_2H_5·HCl	++
XI	C_6H_5-N=C(S-C_2H_5)-NH-C_6H_5	−

(2) Enrico Del Pianto, *Ricera sci.*, **20**, 83 (1950).

(3) M. Solotorovsky, *et al.*, to be published.

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OXIDATIVE PHOSPHORYLATION IN THE CYTOCHROME SYSTEM OF MITOCHONDRIA[1]

Sir:

At least two and probably three phosphorylations are coupled to the passage of a pair of electrons from reduced diphosphopyridine nucleotide to oxygen via the respiratory chain in isolated liver

(1) W. T. Brown, J. H. Quastel, P. G. Scholefield, *J. Appl. Microbiol.*, in press.

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