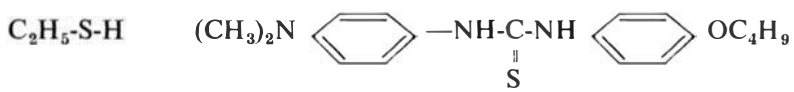
LETTERS TO THE EDITOR

THE EDITOR. RESEARCH DEPARTMENT,
IMPERIAL CHEMICAL INDUSTRIES LTD.,
PHARMACEUTICALS DIVISION,
ALDERLEY PARK, MACCLESFIELD,
CHESHIRE

Dear Sir,

We have had enquiries from several leprologists engaged in the evaluation of new drugs about the possibilities of cross resistance between the thiolesters ("Etisul") and the thioureas (Ciba 1906). This has arisen from a statement made by Dr. Mayer at the Tokio Conference (*Leprosy Review* **30,** 25 (1959).)

He said that "all sulphur containing compounds found since thioureas have apparently similar mode of action. It appears that resistance between them is interchangeable. So if resistance develops, do not substitute one compound for another of this group, but look for compounds with a complete difference in mode of action which does not have CS group". The only interpretation of this statement is that the thioureas and the thiolesters have a similar mode of action and that this similarity is due to the presence of a CS group. The thiolesters such as "Etisul" function by liberation of ethyl mercaptan under the influence of esterases while the thioureas such as Ciba 1906 are effective *per se.* Thus the chemical entities involved are:



Chemically, the sulphur residues in the two compounds are entirely dissimilar: that in ethyl mercaptan resembling the alcohols and that in the thiourea being amidic in nature and being closely related to the thiosemicarbazones which also contain the NH-C-NH residue.
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If the CS group were the significant feature of the two drugs then other thiols such as the methyl and propyl analogues of ethyl mercaptan (CH_3SH and C_3H_7SH) and simpler thioureas such as diphenylthiourea

and thiourea itself $H_2N\,C\,NH_2$ should show some antimycobacterial
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action. In fact, methyl mercaptan is an antagonist of ethyl mercaptan

(against experimental tuberculosis) while the other three compounds have no significant action (against *M. tuberculosis*). If two compounds resemble one another sufficiently to give rise to cross resistance then they must function by the same mode of action: "Etisul" and ethyl mercaptan are not active *in vitro* whereas Ciba 1906 is and it is almost impossible to imagine any metabolite of ethyl mercaptan which could remotely resemble the thioureas. We have been able to produce strains of *M. tuberculosis* which were resistant to "Etisul" but these strains were sensitive to all the known antimycobacterial drugs. We have not tested "Etisul" against *M. tuberculosis* which was resistant to the thioureas but we would expect that it would be effective and Dr. Davey (*Leprosy Review* **30,** 71 (1959)) has found that leprosy patients exhibiting signs of drug resistance to "Etisul" responded to the thiourea and presumably the reverse would be the case. He has also (*Leprosy Review* **30,** 141 (1959)) shown that "Etisul" and the thiourea are compatible in that they prevent the emergence of resistant strains of *M. leprae.*

There is thus no chemical, biological or clinical evidence to suggest that the two groups of compounds might have similar modes of action and that there should be cross resistance to them. On the evidence available, and on theoretical grounds the opposite is the case.

G. E. DAVIES
G. W. DRIVER