dicarboxylic acids, thioglucose and the O-glucoside of dithioglycerol[5]. The last of these compounds, given the name *BAL-Intrav*, proved to be the most promising, and has now been shown to have the following properties: (1) The lethal dose ($L.D._{.50}$) to rats is about 7·5 gm. per kilo. (2) It penetrates very slowly into cells, so that its effective distribution in the body is in the blood and intercellular fluids. It is rapidly excreted in the urine. (3) At a dosage of 1–2 gm. per kilo it causes no pathological symptoms in rats, rabbits, guinea pigs or goats, other than a transient increase in rate of respiration. (4) With all four species it gives marked protection against systemic lewisite poisoning. (5) With rabbits, which were studied in most detail, a total dosage of 1·5 gm. per kilo of *BAL-Intrav* administered by intravenous injection at intervals over 6 hours will give complete protection against 3–4 times the $L.D._{.50}$ of lewisite, even when four hours elapse between contamination and commencement of treatment.

The lewisite dosage (three to four times the $L.D._{.50}$) in the case of rabbits was approximately an $L.D._{.95}$, that is, it killed 95 per cent of the animals in the absence of therapy. The animals died between 10 and 48 hours after contamination. If treatment was delayed for 6½ hours after contamination, about 50 per cent of the animals could be saved. It was thought that the mortality of 50 per cent when therapy was delayed for 6½ hours might be due to tardy removal of arsenic from intracellular sites. It seemed likely that the rate of removal could be increased by giving a small amount of a cell-permeating thiol, such as dithioglycerol (*BAL*), which could act as a carrier of arsenic between the cell and the *BAL-Intrav* in the blood. This proved to be the case; a dose of 4 mgm. per kilo of *BAL*, when given with a high dosage (1–1·5 gm. per kilo) of *BAL-Intrav*, reduced the mortality under the conditions given above to 25 per cent when treatment was delayed for 6½ hours after contamination. A dose of 4 mgm. per kilo of *BAL* produces only transient signs of toxicity, and when given without *BAL-Intrav* did not reduce mortality at all[6].

Prof. R. A. McCance and Dr. E. M. Widdowson have kindly made intravenous injections of *BAL-Intrav* into a number of men, observing no ill effects with a dose of about 100 mgm. per kilo, given as a single intravenous dose. The maximum permissible single dose of *BAL* is 4 mgm. per kilo, at which level some pathological complications appear. (This dose may, however, be repeated at intervals of four hours.)

Those engaged on this problem are deeply indebted to many friends at Oxford, Cambridge and at the Ministry of Supply, both in London and at Porton: the list of names involved is too long to mention here, but an exception must be made in the case of Prof. G. R. Cameron, without whose sympathetic advice and generous practical assistance we should not have accomplished this work. This work was commenced while three of us (J. F. D., M. D. and P. D. M.) were members of a team under the administration of Dr. M. Dixon. We are indebted to the Chief Scientific Officer, Ministry of Supply, for permission to publish this report.

[1] Cameron, Short, Mitchell and Danielli. Report to Ministry of Supply, 1943.
[2] Mitchell, Danielli and Short, Report to Ministry of Supply, 1944.
[3] Peters, Stocken and Thompson, *Nature*, 156, 616 (1945).
[4] Danielli, in "Cytology and Cell Physiology" (ed. Bourne, 1942).
[5] Danielli, Danielli, Mitchell, Owen and Shaw, Report to Ministry of Supply, 1944.
[6] Danielli, Jones and Mitchell, Report to Ministry of Supply, 1945.

AMERICAN WORK ON *BAL*

THE brief review in these columns (*Nature*, 156, 616; 1945) by Peters, Stocken and Thompson giving the history of the discovery and outlines of work upon 2 : 3 dimercaptopropanol (*BAL*, or British anti-lewisite), has now been amplified by a statement from the United States (*Science*, 102, 601; 1945) ably compiled by L. L. Waters and Chester Stock. In the previous article, the main facts were given of the biochemical work leading up to this discovery, and the evidence was briefly summarized for the view that vicinal dithiols are effective antidotes to arsenic through their ability to form ring compounds with trivalent arsenicals, permitting thereby the excretion of increased amounts of arsenic from the system. In the American review, an account is given of the intense programme of study undertaken jointly by various U.S. Government agencies into the preparation and manufacture, biochemistry, toxicology, pharmacology, experimental therapeutics and clinical application of the new discovery.

In addition to confirming and extending the fundamental British observation, American workers have shown how trypanosomes and spermatozoa poisoned with arsenic can be revived by dithiols of *BAL* type, with presumptive elimination of the arsenic. They have studied in detail the action of *BAL* as a reducing agent, finding that it converts methæmoglobin instantaneously to hæmoglobin, and in the presence of oxygen will open the porphyrin ring. Among the pharmacological facts recorded, it has been found that lethal amounts of *BAL* cause an intense vasoconstriction in skin and skeletal muscle with early transient rise in blood pressure; there is also a reduction in *p*H of the blood. In an analysis of the toxicity of the compound when injected in amounts approaching a lethal dose, it was also shown that by keeping cytochrome *C* in a reduced condition it can interfere with cytochrome oxidase activity, and that oxidized *BAL* can act as an inhibitor of enzymes containing —SH groups essential for their activity.

It is perhaps worth stressing that, despite these toxic actions produced by high concentrations of the drug, *BAL* dissolved in peanut-oil has now been injected safely and with favourable results into a large number of patients suffering from arsenical dermatitis both in Great Britain and in the United States. It is stated that animal experiments have shown that *BAL* can prevent the development of pulmonary lesions not only after the inhalation of lewisite, but also after cadmium and zinc fumes; and that it is also active against the systemic action of mercury. Preliminary therapeutic trials in mercury poisoning have been encouraging. The detailed publications will be awaited with interest.

OBITUARIES

Sir Farquhar Buzzard, Bart., K.C.V.O.

SIR FARQUHAR BUZZARD died at Oxford of coronary thrombosis on December 17 in his seventy-fourth year. Like his father, Dr. Thomas Buzzard, of the National Hospital, Queen Square, he was a distinguished neurologist. After graduation from Oxford and St. Thomas's Hospital, he became house physician at Queen Square to the great Hughlings Jackson, an old friend of his family. He was elected to the staff at Queen Square in 1905, and later to St. Thomas's.