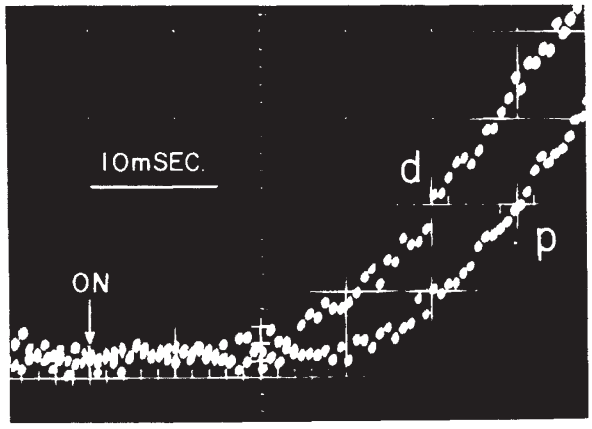

Fig. 2. Commencement of the distal *PIII* (indicated as *d*) and the proximal *PIII* (indicated as *p*), showing the difference in latency. Each of them was summed 70 times in a digital computer. Arrow indicates the beginning of illumination

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PHARMACOLOGY

Drosophila-tests in Pharmacology

IN a communication under this heading, Lüning[1] has suggested a routine procedure by which potentially mutagenic drugs can be screened in tests on *Drosophila*. He uses developmental delay as the type of somatic damage that is likely to be correlated with whatever genetical damage has occurred. I wish to point out that in the only instance in which, to my knowledge, the effects of the same mutagen on developmental delay and mutation frequency were investigated, the correlation between them was clearly and strikingly negative. When larvae are raised on food to which formaldehyde at a low concentration has been added, high mutation frequencies are obtained so long as development proceeds at the normal speed. Any condition that delays development of the treated larvae—be this shortage of food, poor quality of food, supplementary harmful treatments, or even a more than optimal concentration of formaldehyde—concomitantly decreases mutation frequency[2]. For this particular mutagen, therefore, developmental delay would be a highly misleading guide to mutagenicity. It is, of course, possible that formaldehyde is exceptional in this respect, and that Lüning's test might be more reliable for other chemicals. Before this can be assumed, however, it will be necessary to establish experimentally for at least one member of the group of chemicals to be screened that its mutagenic action is positively correlated with its delaying action on development.

As an additional criterion for potential genetic damage, Lüning uses survival to adulthood, which for some of the drugs used by him went down as developmental time increased. This was also the case in most of the experiments with formaldehyde already mentioned. Since in these experiments genetical damage was negatively correlated with developmental delay, it was also negatively correlated with survival, more mutations being obtained at high than at low survival. In a number of cases it was, however, possible to destroy the parallelism between survival and speed of development, and in these it could be shown that the decisive factor in determining mutation frequency was developmental speed rather than survival. This was most clearly shown in one experiment where mutation frequency among the same batch of treated larvae was about twice as high in those flies that had developed with normal speed as in those that had reached adulthood after a developmental delay lasting 5–6 days. Conversely, in one experiment in which developmental delay had been prevented by the presence of dinitrophenol in the culture bottle, mutation frequency was not affected by a highly significant decrease in survival. It would seem, therefore, that decreased survival not correlated with delayed development might be a guide to genetical damage. This would agree with the findings by Müller's group[3] that X-ray-induced life-shortening in *Drosophila* is mainly caused by somatic chromosome loss. One way of demonstrating this consisted of the finding that, for a given exposure of larvae, survival decreased from females to rod-*X* males to ring-*X* males. Parallel results with a given drug would form strong presumptive evidence of genetic damage.

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Synergistic Interaction of Kethoxal *bis*(Thiosemicarbazone) and Cupric Ions in Sarcoma 180

2-KETO-3-ethoxybutyraldehyde *bis*(thiosemicarbazone) [kethoxal *bis*(thiosemicarbazone); KTS], an agent that chelates metals of the first, second and third transition series[1], has been reported to be an inhibitor of the growth of several transplanted rodent neoplasms[2–5]. The antineoplastic potency of KTS was enhanced by the presence of either cupric or zinc ions[6]; however, the preformed cupric chelate was found to be the most potent of several different metal chelates of KTS[1,5,7]. To investigate the relationship of copper ions to the antineoplastic activity of KTS, the effects of combinations of cupric ions (as cupric chloride) and KTS, both on growth and on the synthesis of nucleic acids and proteins, were measured in sarcoma 180 ascites cells.

The tumour-inhibitory effects of such combinations on neoplastic growth were measured by determining the survival time of adult *Ha/ICR* Swiss mice inoculated with approximately 4×10^6 sarcoma 180 ascites tumour cells by intraperitoneal injection as previously described[8]. Therapy was initiated 24 h after implantation of the neoplastic cells and was continued for six consecutive days. The results obtained are shown in Table 1. Neither KTS in daily doses up to 60 mg/kg, nor cupric chloride in daily doses up to 10 mg/kg, increased the average survival time of tumour-bearing mice. In combination, however, significant prolongation of life was produced at low levels of each drug. No concomitant toxicity to the host was evident; thus, no weight loss from onset to termination of therapy was observed.

To probe for metabolic alterations associated with the growth-inhibitory potency of combinations of cupric chloride and KTS, the effect of a single dose of these agents on the synthesis of DNA, RNA and proteins was