Good frozen-dried preparations for electron microscopy can be made easily in the following way: Aluminum strips are substituted for glass microscope slides in mounting the usual collodion- or formvar-covered screens. When ready for use, these metal slides and the screens they carry are placed on a block of metal (approximately $8 \times 3 \times 2$ cm.), precooled with dry ice or liquid air. When a microdrop of solution is applied to, and immediately withdrawn from, screens cooled in this fashion, some will instantly freeze; a tissue such as tendon, touched momentarily to a cold screen, will leave frozen shreds behind. The collodion or formvar substrate can often be omitted when dealing with tissues and with suspensions of elongated particles. The block has sufficient thermal capacity to hold the preparations frozen while they are being made, while both block and preparations are being transferred to a vacuum chamber, and until a high vacuum has been drawn. If the preparations are to be shadow-cast before microscopic examination, vacuum desiccation and shadowing can conveniently take place in the same apparatus without breaking vacuum. The screens on their metal block must remain well below freezing until desiccation has been completed, but by the end of the run they should be warm enough so that moisture from readmitted air does not condense on them. The slow thermal leakage this demands is provided by putting the block on one or more pieces of lightly metal-coated glass.

Electron micrographs have thus far been made of frozen-dried bacteria, of several plant and animal viruses, and of certain tissues. With dilute solutions of the tobacco mosaic and bean mosaic viruses, for example, these pictures are indistinguishable from those of ordinary air-dried preparations; in such instances it would appear that air-drying does not appreciably distort the virus particles. Influenza virus particles have been strikingly full and turgid after freeze-drying. Unusually interesting pictures have been obtained from frozen-dried concentrated solutions of tobacco mosaic protein. In them many rods are associated together in two dimensions to yield areas which look surprisingly like sheets of connective tissue and break up in the same way into fibrous bundles—for example, under impact of the electron beam. Frozen-dried preparations containing appreciable quantities of salt have not yet given useful micrographs, because in its extreme dispersion this salt tends to smear over the fine details that are present.

In this laboratory frozen-dried as well as air-dried preparations are now a routine. Electron micrographs of some of them will shortly be published elsewhere.

Letters to the Editor

On the Mechanism of Action of Folic Acid and Liver Extract in the Treatment of Anemia

In view of the discovery by Spies and co-workers (*S. med. J.*, 1945, 38, 707) that synthetic folic acid has antianemic action in the treatment of human macrocytic anemias, the question of its mechanism of action has become a matter of some interest. Experiments performed in our laboratory (details to be published) may throw considerable light on this problem.

We have produced significant hyperchromic anemias in five normal dogs by the subcutaneous injection of 3 mg. of acetylcholine bromide twice daily for 47 days. Two of these dogs were then treated by the daily injection of liver extract, in addition to acetylcholine. They responded with an increase of reticulocyte percentage and a gradual regeneration of red blood cells to their normal number. Another dog of this series received daily folic acid injections (2 mg.) and responded in a similar manner.

Three dogs were made anemic by the feeding of choline chloride according to the general method reported previously by the author (*Amer. J. Physiol.*, 1944, 142, 402). Two of these dogs were treated with daily injections of folic acid and the third, after serving as an anemic control animal, was treated daily with liver extract. These animals all responded by showing a rise of reticulocytes (to peaks of 3.4–4.2 per cent, from 6 to 9 days after onset of treatment) and a return to normal of their erythrocyte numbers within 20 days, in spite of continued choline feeding.

During anemia, acetylcholine-like activity was detected in extracts of serum of blood drawn from the "choline anemia" dogs at one and one-half hours after the administration of 200 mg. of choline chloride. This activity was markedly diminished after antianemic treatment had been instituted. Cholinesterase activity (determined by an electrometric titration method) of the serum of one dog tested was low during anemia and was increased 12-fold during treatment with liver extract.

Incubation of various dog blood sera with folic acid or liver extract at 37° C. increased their cholinesterase activities by from 0 up to 93 per cent. Similar incubation of one normal human serum with liver or folic acid increased its activity by 15 per cent.

Oral administration of 5–7.5 mg. of folic acid to two normal human subjects increased their serum cholinesterase activities by 33 and 16 per cent within five hours.

It is concluded from these experiments that liver extract and folic acid act by increasing, in some manner, the formation of cholinesterase in the body.

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Some Effects of Electronic Transitions Upon Precision Thermometry

Recent measurements of the electrical resistance of various materials at elevated temperatures have disclosed the following information which may be of value in precision thermometry:

(1) The electrical resistance of a pure conductor is a straight-line function of temperature, but the slope changes appreciably between certain specific temperatures.

(2) Since the temperatures at which these discontinuities have been found are independent of purity, concentration, or heat treatment, the resistance-temperature curve for an alloy will be affected to some extent at each of the temperatures which are characteristic of each of its components. These temperatures may be used as an accurate method of calibration in the proper temperature range. The discontinuities in the curve for carbon, for example, are particularly satisfactory for calibration in the range above the melting point of gold.

(3) Errors may be introduced in certain ranges of temperature by the common practice of drawing calibration curves smooth instead of as straight lines changing in slope at these specific temperatures. These errors may be as large as 6° C. in a chromel-alumel thermocouple or as large as 2° C. in a platinum resistance thermometer. The chromel-alumel thermocouple is free from these errors below about 160° C., and the platinum thermometer is not affected markedly except in the range 160°–932° C., most of the trouble being between 160° and 800° C.

(4) Heat treatment is equally as important as purity in affecting the temperature coefficient of resistance for platinum. Depending upon the heat treatment, values of the coefficient as high as 1.400 or as low as 1.366 have been secured, using the same specially prepared high-purity wire.

Further information on these points will be published in the near future.

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Some Thoughts on "Gene Action"

Dr. Deakin's recent letter (*Science*, 1946, 103, 570–572) prompts me to add some thoughts which I noted down some time ago on the same subject. I am presenting them merely in the hope that they may invite extended discussion of this problem.

It has been generally accepted that the control of hereditary factors is closely associated with the desoxyribonucleic acid (DRA)—protein components of the chromosomes. A widely held concept has attributed to these components the ability of catalyzing enzyme processes or has assigned to them a principal role in the production of enzymes. In view of some recent work, however, the question may be raised whether all action (or some action) of DRA may not be in the nature of *inhibiting* enzyme processes, either qualitatively or quantitatively. Among the recent work to which this might be applied are the data by Avery and co-workers on the specific transformation of bacterial types of DRA, the data by Dickinson on the suppression of bacterial mutation through enzyme inhibitors, as well as the results of Lindegren on yeast and Sonneborn on *paramecium*. Furthermore, *in vitro* tests by Greenstein have actually demonstrated the ability of DRA to inhibit enzyme reactions. If the action of DRA in the chromosomes is totally or partly of an inhibiting nature, it implies that the extrachromosomal material contains many more ultimately possible enzyme reactions than those actually realized during the development and life of an organism, since many of them would be blocked by the chromosomal constituents. This block may or may not be a total one. The inhibition may be in some cases a quantitative one, delaying time and amount of action of a particular enzyme. A loss in DRA would result in the release of one or more additional enzymatic processes. This possibility may be realized in the well-known mutation due to chromosomal deficiencies. This concept would assign a much greater importance to extrachromosomal constituents than has hitherto been customary. Extrachromosomal constituents, as long as they remain stable, would limit the extent of variation possible through changes in the chromosomes, since the ultimately possible enzyme reactions would theoretically be exhausted if none of them is blocked by chromosomal constituents (microevolution). However, changes or extrachromosomal constituents may occur, but far less frequently than changes of chromosomal constituents. Such changes would then permit the realization of completely different enzyme processes, dependent on the extent of their quantitative or qualitative inhibition by chromosomal constituents (macroevolution).

Incidentally, the inhibiting-factor hypothesis is not altogether a new concept. Bateson, for example, speculated along these lines as early as 1913 (*Problems of genetics*. Yale Univ. Press, esp. pp. 94–96).

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Meteor Crater, Arizona

In December 1945 Nelson H. Darton restated to the Geological Society of America, and also to the Association of American Geographers, his belief that Meteor Crater, east of Flagstaff on the Arizona Plateau, is of volcanic rather than meteoritic origin. He cited a decision of the U. S. Board on Geographic Names in which the name *Crater Mound* was officially adopted, and he urged that the use of the term *Meteor Crater* be discontinued. Since notices of Mr. Darton's views have been published in *Science News Letter* and other nontechnical media, it seems timely to indicate that the majority of geologists,