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DEPARTMENT OF PHARMACOLOGY

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Dr. Arthur H. Kornberg
Department of Biochemistry
Stanford University
Palo Alto
California

Dear Arthur:

Thank you very much for your very kind note regarding your recent honors. I hope you enjoy the trip to Sweden, and that you are able to take advantage of Swedish hospitality from now on. I understand this is one of the additional rewards.

Quite recently, while examining some effects of several drugs on nucleic acid synthesis, I made an observation which surprised me, but which I have been able to reproduce several times since then. Labeling Bacillus cereus with uracil leads to the formation of radioactive pyrimidines in RNA and DNA. We have recently worked out a procedure involving membrane filters and KOH hydrolysis where we may separate RNA from DNA quantitatively and most reproducibly. As a result we have a sensitive way for assaying quickly the incorporation from a labeled compound into these macromolecules. The surprising feature came up in an experiment where cells grown with C^{14}-uracil were centrifuged and resuspended so as to remove the label and were then allowed to continue growing. During this time, measurements were made on the relative incorporations into RNA and DNA. Since, after the centrifugation no isotope was present in the medium, it was reassuring to observe that the total radioactivity per ml. of bacterial suspension remained constant. However, the relative radioactivity in the DNA fraction continued to rise, apparently at the expense of that in the RNA. This would mean that cells normally growing after the resuspension seem to take bases from the RNA and converting them into the DNA.

Similarly, cells, after a period of growth as above, were allowed to stand at room temperature rather than being centrifuged and resuspended, and an identical observation was made. During this standing process I doubt if any DNA was being synthesized, but nevertheless, the relative activity in the KOH-insoluble residue (apparently DNA) kept increasing for a time.

This phenomenon was also observed while standing with exogenous uridine plus uracil. Similar observations were made when P^{32} was used as the label. Thus degradation to nucleosides would be excluded. I am enclosing two graphs of these results.

I am writing you to find out if you have made similar observations. It may be that I am overlooking something very simple, but then again, it might be a useful tool for analyzing DNA synthesis. I can see no reason why the technique should not be an adequate measurement of DNA synthesis, since it has never failed us in the past. One other possibility might be a breakdown of RNA, perhaps to the pyrophosphates which are then converted to the corresponding deoxy derivatives, phosphorylated, and incorporated into DNA. The drugs (azaguanine and chloromycetin) had no influence on this observation, but allowed it to be made more clearly because growth was inhibited, although nucleic acid synthesis was not.

I would be interested to hear any comments that you might have in this regard.

With best wishes,

H. George Mandel
Professor of Pharmacology

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