

**Baddiley J, Lythgoe B, McNeil D & Todd A R.** Experiments on the synthesis of purine nucleosides. Part I. Model experiments on the synthesis of 9-alkylpurines. *J. Chem. Soc.* 1943:383-6; **Atherton F R, Openshaw H T & Todd A R.** Studies on phosphorylation. Part I. Dibenzyl chlorophosphonate as a phosphorylating agent. *J. Chem. Soc.* 1945:382-5; and **Baddiley J & Todd A R.** Nucleotides. Part I. Muscle adenylic acid and adenosine diphosphate. *J. Chem. Soc.* 1947:648-51.  
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These papers developed methods for the structural determination and synthesis of nucleosides and nucleotides, the building blocks of the genetic code, with a special emphasis on specific phosphorylation and polyphosphorylation procedures. [Editor's note: We have identified 118 papers by Lord Todd and coauthors, on the subjects of nucleosides, nucleotides, and phosphorylation. There are more than 5,300 citations to these papers in the *SCI*<sup>®</sup>, 1945-1989.]

## Nucleotides, Nucleotide Coenzymes, and Phosphorylation

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The series of researches on "nucleotides and nucleotide coenzymes," which was recognized by the award of the Nobel Prize for chemistry in 1957, really had its origin in my work on the structure and synthesis of vitamin B<sub>1</sub>, carried out with Franz Bergel and a small group of junior research workers in Edinburgh between 1934 and 1936. I was fascinated by the fact that B<sub>1</sub> could exert such striking effects when administered in extremely small amounts and decided I would try to ascertain the structural features responsible for this remarkable property.

I decided that studies on the mode of action of vitamins would be more appropriately carried out using analogues of coenzymes rather than of simple vitamins and that I should turn my attention to the synthesis of these coenzymes and their analogues. Most of the coenzymes appeared to contain nucleotide residues, and so it was clear that if I wished to make progress in this endeavour I would have to enter entirely new fields and develop methods for the synthesis of nucleosides and nucleotides and devise a range of procedures for phosphorylation,

polyphosphorylation, and the linkage of molecules through phosphate and polyphosphate groups.

Obviously, to do this would involve an ambitious research programme that would absorb a large amount of resources in time and manpower, and I therefore had to wait until I had a position of some permanency with access to a substantial group of co-workers (both pre- and postdoctoral) if my plans were to have any hope of realization. Fortunately, I was given this opportunity when I was appointed to the Chair of Chemistry in Manchester in 1938 and was able to make a start on my programme, despite limitations on available time and manpower imposed by the outbreak of war in 1939.

The term "nucleoside" was applied at that time to eight N-glycosides obtained by hydrolysing nucleic acids, of which latter only two were believed to exist—one from plant sources (ribonucleic acid) and the other from animals (deoxyribonucleic acid); the belief that only two existed was due to the fact that all samples of each type—i.e., of vegetable or animal origin—were amorphous, were uncharacterizable by then existing methods, and seemed always to yield the same basic nucleosides in equal amounts.

In 1938 I was not practically interested in nucleic acids, apart from the fact that they yielded nucleosides that were essential raw materials for the synthetic work leading to nucleotide coenzymes, which was my prime object. I therefore began my work in Manchester using a three-pronged approach: (1) The synthesis and final clarification of the structure of the natural nucleosides. (2) The development of methods for the phosphorylation and polyphosphorylation of nucleosides, i.e., nucleotide synthesis. (3) The linkage of nucleosides and other molecules through phosphate and polyphosphate groups, i.e., the final stage in coenzyme synthesis. These researches continued without serious interruption at the University of Cambridge, to which I moved from Manchester in the autumn of 1944.

It may well be asked why the chemistry of the simple nucleotides—the phosphates of the nucleosides—was not further advanced, especially as we recognize today that they occupy a central place in the chemistry of the living cell. True, their significance was long unrecognized and emerged only very slowly as biochemical research got into its stride, but I believe that a much more important reason is to be found in the physical properties of compounds of the nucleotide group. As water soluble compounds with no proper melting points, they were extremely difficult to handle and to characterize by the classical techniques of organic chemistry; and their study was accordingly most discouraging to early workers. This was certainly the position when we be-

gan our work in the field but thereafter over a period of years there appeared new experimental techniques such as paper and ion-exchange chromatography, paper electrophoresis, countercurrent distribution, and the application of ultraviolet and infrared spectroscopy to structural studies. Had these new techniques not appeared at the time, I doubt whether our work would have been possible, let alone successful.

Our work was particularly directed to the synthesis of the purine nucleosides in order to prove, as we did, that the sugar residue in adenosine (and guanosine) is attached to the 9-position in the purine system. This work (published in some 26 papers between 1943 and 1949) finally established that the ribonucleosides adenosine and guanosine are 9- $\beta$ -D-ribofuranosides of adenine and guanine, respectively, and that uridine and cytidine are 3- $\beta$ -D-ribofuranosides of uracil and cytosine, respectively.

From the outset it was clear to us that flexible and specific methods for the phosphorylation and polyphosphorylation of nucleosides and related compounds would be essential to our work and, over a period of some 16 years (1945-1961), we published 26 papers on this topic, mainly in the *Journal of the Chemical Society*.

By the application of effective phosphorylation methods, we were able in due course to synthesize unambiguously all the simple nucleotides derived from the nucleosides obtained from ribonucleic acids. As a result we were ready to proceed to our projected studies on synthesis of nucleotide coenzymes.

Our work on nucleotides (including nucleic acids themselves) was published in a series entitled "Nucleotides," published in 46 papers between 1947 and 1961, mainly in the *Journal of the Chemical Society*.

During these studies we synthesized several important coenzymes—adenosine triphosphate (ATP), flavin adenine dinucleotide (FAD), co-enzyme (NAD), coenzyme 11 (NADP), and uridine-diphosphate-glucose (UPG)—and established firmly that nucleic acids are 3':5'-linked polynucleotides. The chemical structure of the nucleic acids was thus for the first time clearly established (1951), and we paid little further attention to them. Determination of the sequence of nucleotide residues in individual nucleic acids would require splitting the macromolecules specifically into small pieces and proceeding as Sanger was doing in his monumental work on protein structure. He was, indeed, later to apply his methods with great success in the polynucleotide field, but we had no experience in that type of work and so did not pursue it, although we showed that stepwise degradation of polynucleotides could be effected by periodate oxidation. Equally, although we assumed that, because of their stability, it would be the deoxyribonucleic acids that transmitted hereditary characteristics, we did not pursue that aspect of the matter further.

The nucleic acids were, to us, simply the source of nucleotides and nucleosides that we required for nucleotide coenzyme studies. We were, of course, interested in a general way in their function; we were aware of, and followed, the beautiful analytical work of E. Chargaff,<sup>1</sup> but we, like many others, did not realize its full significance. We were, of course, aware that if deoxyribonucleic acid was the genetic material then some kind of template mechanism must exist for its reproduction; but methods of that nature were, as far as we were aware, as yet unknown in synthetic chemistry, and we paid little or no attention to that problem. It was only a year or two later (1954) that J.D. Watson and F.H.C. Crick produced their brilliant interpretation<sup>2</sup> of X-ray structural studies of deoxyribonucleic acid and opened up the whole field of genetics by their picture of the acid as a double helical structure of two complementary polynucleotide chains held together by an obligatory pattern of hydrogen-bonding between nucleoside residues. This, of course, gave an immediate and manifestly correct explanation of the mechanism whereby genes constructed of deoxyribonucleotides can reproduce by a template mechanism and so play a fundamental role in genetics.

The work described in this article was carried out in the period between 1938 and 1957 but was not carried further by me. For this there were several reasons. First, I had rather lost faith in my original idea that I could really make much progress in understanding vitamin specificity through the very arduous procedures of coenzyme synthesis and, secondly, it seemed clear that nucleotide studies would rapidly become part of molecular biology rather than organic chemistry. Moreover, I was, at that particular time, heavily involved in the chemistry of vitamin B<sub>12</sub> and in the study of a fascinating series of colouring matters that occur in aphids. Finally, and not by any means least importantly, my group of coworkers, who had with me developed the nucleotide field, by chance began to disband rapidly, its members (all of them young) leaving to take up senior posts in industry or in the academic world. Some prominent members later continued to develop studies in the nucleotide and related fields, e.g., D.M. Brown, H.G. Khorana, and A.M. Michelson, but most turned (successfully, I am glad to say) to fresh fields, such as the discovery of teichoic acids in the case of James Baddiley.

Somewhat similar reviews of this work have been given in the past in a variety of lectures and published articles and much of it is to be found in my 1957 Nobel Lecture.<sup>3</sup>

[Editor's note: The distinguished organic chemist Lord Todd of Trumpington is Chancellor of the University of Strathclyde, Glasgow, Scotland. He was the sole winner of the Nobel Prize for chemistry in 1957 for his work on nucleotides and nucleotide coenzymes.]

1. Chargaff E. Isolation and composition of the deoxypentose nucleic acids and of the corresponding nucleoproteins. (Chargaff E & Davidson J N, eds.) *The nucleic acids: chemistry and biology*. New York: Academic Press, 1955. Vol. 1. p. 307-71. (Cited 470 times.)
2. Crick F H C & Watson J D. The complementary structure of deoxyribonucleic acid. *Proc. Roy. Soc. London Ser. A* 223:80-96, 1954. (Cited 240 times.)
3. Todd A. Synthesis in the study of nucleotides. *Les Prix Nobel en 1957*. Stockholm, Sweden: Norstedt & Söner, 1958. p. 119-33.