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William Astbury and the biological significance of nucleic acids, 1938–1951

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ABSTRACT

Famously, James Watson credited the discovery of the double-helical structure of DNA in 1953 to an X-ray diffraction photograph taken by Rosalind Franklin. Historians of molecular biology have long puzzled over a remarkably similar photograph taken two years earlier by the physicist and pioneer of protein structure William T. Astbury. They have suggested that Astbury's failure to capitalize on the photograph to solve DNA's structure was due either to his being too much of a physicist, with too little interest in or knowledge of biology, or to his being misled by an erroneous theoretical model of the gene. Drawing on previously unpublished archival sources, this paper offers a new analysis of Astbury's relationship to the problem of DNA's structure, emphasizing a previously overlooked element in Astbury's thinking: his concept of biological specificity.

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0. Introduction

'The instant I saw the picture my mouth fell open and my pulse began to race. The pattern was unbelievably simpler than those obtained previously ('A Form'). Moreover, the black cross of reflections which dominated the picture could only arise from a helical structure'.[1] So wrote James Watson in *The Double Helix*, recalling the moment in January 1953 when Maurice Wilkins first showed him an X-ray photograph of B-form deoxyribonucleic acid (DNA).[2] The photograph had been taken in May 1952 by Rosalind Franklin at King's College, London (Fig. 1a).[3] The cross pattern it showed—which Watson recognised as characteristic of helical structure—provided an essential clue in solving the structure of DNA. Yet the Franklin photograph was not the first to show that pattern. In 1951, Elwyn Beighton, a research fellow at Leeds University, had taken similar X-ray photographs of B-form DNA that clearly showed the same central cross feature (Fig. 1b). Beighton's supervisor was the textile physicist turned molecular biologist William T. Astbury, by that time an internationally renowned figure in X-ray crystallographic studies of biological materials. In Astbury's Leeds, however, no one made the leap that was to be the making of Watson.

The apparent neglect of Beighton's work by Astbury has been the subject of debate among historians of molecular biology. On the one side is Pnina Abir-Am, who has suggested that Astbury actually had very little genuine interest in biological problems, and that, despite 'having produced some of the best pictures of proteins and DNA . . . he had failed to keep abreast of the latest biological findings which could have given meaning to his physical results'.[4] In short, for Abir-Am, Astbury was too much of a physicist to appreciate the significance of Beighton's photographs, much less interpret them. On the other side is Robert Olby, who has claimed that Astbury was both interested in biological problems and well aware of major contemporary developments in this area.[5] By way of evidence, Olby cites a letter in early 1945 from Astbury to Oswald

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[1] Watson (1986, pp. 132, 133).

[2] The polynucleotide helix of DNA can adopt three possible conformations termed A, B and Z, which differ according to features such as the distance required to make a complete helical turn (the 'pitch'), the alignment of the deoxyribose groups, and the angle of tilt that the base pairs make with the helical axis. The B-form is longer and thinner and is the form usually assumed in solution, and hence in the intracellular environment. The A-form by contrast is usually found in conditions of low hydration and tends to be more crystalline. Since the goal of nucleic acid work was to understand how DNA functioned within the cellular environment, it was the B-form that was most desirable for X-ray work. One of the main reasons why Bell's pictures did not yield more structural data was that they were a mixture of A and B forms.

[3] Franklin & Gosling (1953).

[4] Abir-Am (1982, p. 356).

[5] Olby (1984).

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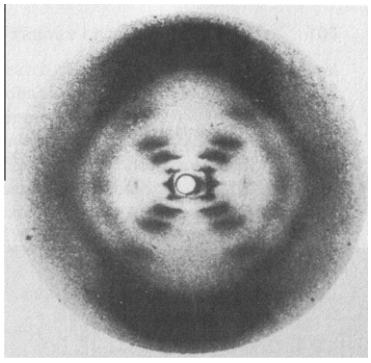

Fig. 1a. X-ray diffraction photographs taken by Rosalind Franklin of B-form DNA in early 1952. The central cross-pattern was immediately recognised by Watson as being characteristic of a helical structure. (From Franklin & Gosling, 1953).

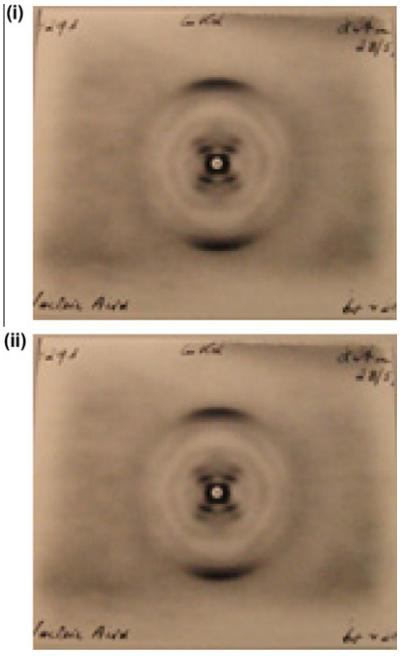

Fig. 1b. X-ray diffraction photographs taken by Elwyn Beighton in Astbury's laboratory of B-form sodium thymonucleate fibres on (i) 28th May 1951 and (ii) 1st June 1951. A striking feature of both pictures is the same central cross-pattern seen in Franklin's photograph shown above. (MS419, Box C.7, Astbury Papers, Special Collections, Brotherton Library, University of Leeds. Reproduced with kind permission from Special Collections, Brotherton Library, University of Leeds).

Avery, a clinician at the Rockefeller Institute. During the previous year, Avery together with his colleagues MacLynn McCarty and Colin MacLeod, had identified nucleic acid as being the chemical factor responsible for heritable changes in the pneumococcus bacterium. As is clear from the letter, this discovery caused Astbury much excitement and he asked Avery to send a sample of the purified nucleic acid to Leeds for study by X-ray analysis. For Olby, then, Astbury's problem was not lack of biological nous, but something else: his theory of the gene. Astbury backed the nucleoprotein model or theory of the gene, which posited that genes were constituted of both DNA and proteins. In Olby's view, it was this erroneous theory that held Astbury back, leaving him incapable of appreciating the full significance of Beighton's photographs.

Here I wish to endorse part of Olby's case and dissent from another part. The 1945 letter to Avery should put to rest the charge that Astbury was largely uninterested in biology. What remains questionable, however, is whether subscribing to the nucleoprotein model of the gene explains Astbury's failure to beat Watson and company to the double helix. In what follows I aim to show, contrary to Olby, that the model as Astbury understood it was far more flexible than tends to be remembered, and could well have accommodated the notion that DNA functions by itself, without help from proteins. Relatedly, I want to suggest that new insight into Astbury's case can be gained if, in line with more recent scholarship, we shift attention from the era's models of gene composition to its concepts of biological specificity—of how, that is, the structures of biological molecules determine their specific functions. Astbury's contact with Avery and response to his work—preserved in previously unexamined correspondence as well as unremarked passages in the 1945 letter—turn out to provide an invaluable window onto Astbury's understanding of biological specificity, how it related to this conceptual shift and how it helps explain his failure to make more of Beighton's photographs. At the outset, however, it is necessary to review Astbury's work in the 1920s and '30s on the structure of proteins.

1. Prewar X-ray crystallographic studies: macromolecular conformation and biological specificity

Having trained in X-ray crystallography at the Royal Institution under Sir William Bragg, Astbury was appointed lecturer in textile physics at Leeds University in 1928, where he was charged with the task of using X-ray diffraction to study the structure of wool fibres. A major result of this work was the demonstration that the elasticity of wool fibres could be accounted for by changes in molecular structure. As a wool fibre was stretched, the constituent keratin polypeptide chains underwent a conformational change from a folded form (which he termed 'α-keratin') to an extended (β) form.

Emboldened by his findings with wool fibres and having attracted the support of the Rockefeller Foundation, he then went on to show, in a series of landmark papers beginning in 1931, that a similar conformational change could explain the elastic properties of other keratinous biological fibres such as hair and feather.[6] Nor were such elastic properties confined only to fibres made of keratin, for Astbury then demonstrated that myosin, the chief molecular component of muscle tissue, underwent a similar transition from a folded α- to an extended-β form, a conformational change which he speculated might explain the contractile properties of muscle.[7] This conformational change was also observed in fibrous proteins of the epidermis and the key blood clotting component fibrinogen, leading to the classification of these different fibres as the keratin-myosin-epidermal-fibrinogen (k-m-e-f) group.[8] Astbury had thus demonstrated not only that the macroscopic properties of biological materials could be explained by changes in structure at the molecular level, but that apparently diverse biological materials were united by an underlying common conformational change. Here were the crucial innovations underpinning what gradually came to be called 'molecular biology'—a phrase that Astbury was one of the first to use.[9]

[6] In a biographical memoir written in 1963, the crystallographer J.D. Bernal, cited the following three papers as being 'key' to Astbury's work—Astbury & Street (1932), Astbury & Woods (1934), Astbury & Sisson (1935).

[7] Astbury & Dickinson (1935a,b), Astbury & Dickinson (1940).

[8] Astbury, Bailey, & Rudall (1943).

[9] Although Astbury popularised 'molecular biology' in the United Kingdom, the origin of the term has actually been credited to Warren Weaver at the Rockefeller Institute (Judson, 1996, pp. 52–53).

His conviction that changes in structural conformation were central to any understanding of biological systems was a key theme of exhaustive studies carried out by his PhD student Florence Bell (later to become Mrs. Sawyer) between 1938 and 1939 on a diverse range of polysaccharide and protein fibres.[10] In her PhD thesis, Bell also attempted to address the question of whether the properties of the other main group of natural fibrous proteins, the collagen group, found in tissues such as tendons and the elastoidin component of sharks fin, could be explained by structural changes similar to the k-m-e-f group.[11] A further challenge was the structure of non-fibrous or globular proteins such as ovalbumin, which Bell also studied in her thesis. Although it was known that, on denaturation, such proteins assumed an extended chain form like that of a β-keratin fibre, it was not clear how the polypeptide form of these proteins was folded up in the native state.

The greatest proportion of Bell's doctoral thesis, however, was concerned not with the structure of proteins but with that of another set of biological fibres: the nucleic acids. It was already well understood at that time that the two biological entities known to be capable of self-replication, chromosomes and viruses, were composed of protein and nucleic acid; and this in turn had led to speculation that the relationship between these two compounds was central to an understanding of life. As Bell herself wrote in 1939: 'Possibly the most pregnant development in molecular biology is the realisation that the beginnings of life are closely associated with the interaction of proteins and nucleic acids.'[12] Bell took X-ray photographs of nucleic acids from a variety of different sources including yeast, pancreas and Tobacco Mosaic Virus, but it was her work with fibres of sodium thymonucleate (later to be known as DNA) which yielded the most information. The key feature of Bell's X-ray photographs was a regular repeating structure at intervals of 3.4 Angstroms which led her and Astbury to deduce that this must be the distance between individual nucleotide bases in the molecule. With additional optical data, they therefore proposed a structural model in which the thymonucleic acid fibre was a rigid column of nucleotide bases stacked on top of each other like a 'pile of pennies' (Fig. 2).

As well as enabling the first structural model of thymonucleic acid, the 3.4 Angstrom spacing identified by Bell had some exciting implications, for it corresponded almost exactly with the interval between the side-chains of neighbouring amino acid residues in the extended β-keratin polypeptide chain. For Astbury this correspondence of distances could not have been mere coincidence and, as he explained in a 1938 paper, might well be of profound significance:

> The significance of these findings for chromosome structure and behaviour will be obvious. It seems difficult to believe that it is no more than a coincidence that thymonucleic acid consists of a long succession of nucleotides spaced at a distance so nearly equal to that of the long succession of amino-acid residues in a fully extended polypeptide. Rather it is a stimulating thought that probably the interplay of proteins and nucleic acids in the chromosomes is largely based on this very fact, and that some critical stage in mitosis, involving elongation of the protein chains, is realized in close co-operation with the dominating period of the interacting nucleotides.[13]

In a similar vein, Bell, writing much later, recalled:-

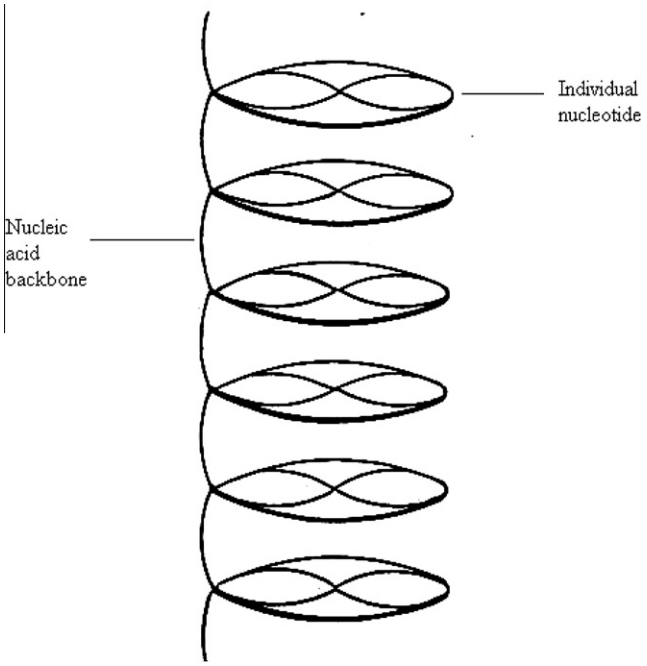

Fig. 2. Astbury and Bell's 'Pile of Pennies' representation of the column of nucleotides constituting the unit of thymonucleic acid. Taken from Astbury and Bell (1938b).

> We were 'ecstatic' to find a spacing identity-but not really surprised, because we had been hoping to find some relationship. Astbury considered that the nucleic acids were templates for protein duplication and organization, and held the polypeptide chains stretched and parallel for the division process.[14]

Astbury and Bell speculated that this similarity in spacing might allow the phosphate groups of a nucleic acid fibre to interact with the side-chains of an extended polypeptide chain, allowing the formation of a nucleic acid/protein fibre. In an initial attempt to explore this possibility they then went on to create complexes of the polypeptides clupein and edestin with nucleic acid fibres, going on to show that X-ray analysis of such compounds gave rise to diffraction patterns characteristic of a fibre. Knowing that chromosomes were composed chiefly of protein and nucleic acid, they proposed that these results provided, in the words of their 1938 paper presented at Cold Spring Harbor, 'a reasonable molecular basis for the linear sequence of genes demonstrated by the cytologists.'

That the material components of the gene should involve proteins to some degree was hardly surprising to them. Nucleic acids had long seemed far more limited in their capacity for structural variation than proteins, having neither the different side-chains nor folding configurations of protein molecules. Early chemical analyses of thymonucleic and yeast nucleic acids had shown the molar ratios of their four constituent nucleotides to be roughly equal to one, leading to the suggestion that both kinds of nucleic acid must consist of repeating units in which these four nucleotides were covalently bonded to each other. As methods for measuring molecular weights improved, successive measurements

[10] Astbury & Bell (1939).
[11] Bell (1939, Ph.D. Thesis).
[12] Ibid, p. 63.
[13] Astbury & Bell (1938a, p. 747).
[14] Sawyer (1967)—cited in Olby (1994, p. 67).

yielded ever larger estimates for the molecular weight of nucleic acids leading to the conclusion that they were formed by the polymerisation of large numbers of individual tetranucleotide units. Although first proposed in 1910, the most commonly cited source for this 'tetranucleotide hypothesis' is a paper by Levene and Bass in 1931.[15] Its effect was to make nucleic acids appear rather biologically inert and unlikely candidates to be the material carriers of hereditary traits. After all, how could a monotonous repetition of four nucleotides in the same order encompass sufficient structural variation to confer diverse phenotypes such as eye colour in the fruit fly Drosophila?

We must take care, however, not to overstate the influence of the tetranucleotide hypothesis and its effect on the perception of nucleic acids. Contemporaries appreciated that the theory was, as a recent commentator has put it, 'almost data-free', based largely on theoretical estimates of nucleotide composition or experimentally derived values of dubious accuracy due to well-understood limitations in the chemical techniques then available.[16] Like many others, Astbury was accordingly cautious about deferring to the theory. Indeed, on the basis of his own X-ray data, he was willing to question the idea that the nucleic acid chain might simply be composed of repeating tetranucleotide units. In the 1938 Cold Spring Harbor paper, he wrote:

> The actual order of sequence of the nucleotides in the column is still unknown, but already the X-ray data raise the question of what interpretation should be attached to the present verdict of analytical chemistry, that only four different nucleotides are used, for the true period along the long axis seems to be at least seventeen times the thickness of a nucleotide. The four nucleotides can therefore hardly follow one another always in the same order.[17]

This last sentence offers a vital but hitherto overlooked clue to Astbury's thinking about nucleic acids at this time. The first thing to note is that behind his reference here to the order of the nucleotides is a particular concept of biological specificity. It had been known for some time that proteins such as enzymes and antibodies were highly specific in their action: particular enzymes acted only on certain substrate molecules and particular antibodies bound only to certain antigen molecules. Since the crystallisation of urease by James Sumner in 1926 and pepsin by John Howard Northrop four years later, enzymes had been understood as composed of regular three-dimensional structures, the particular shape of which dictated their specificity for a given substrate molecule. Furthermore, in 1940, Linus Pauling proposed a theory of antibody action in which their binding to specific antigens was explained in terms of three-dimensional molecular conformation.[18] A view therefore became prevalent that biological specificity in macromolecules was a direct result of their particular three-dimensional structure.

Since they could be composed of as many as twenty different varieties of amino acid, it was easy to see how the three-dimensional folding of a polypeptide chain could generate a protein macromolecule with specific properties such as an enzyme or an antibody. On the face of it, the case of nucleic acids could not have been more different. It was difficult to envisage how a repetition of only four nucleotides could generate structural variation to a similar degree to that seen in proteins. And yet, in the passage quoted above, Astbury indicated that he had glimpsed a way. His interpretation of his X-ray data suggested that there might be irregularity in the nucleotide sequence, and that this irregularity might well give rise to some degree of three-dimensional structural variation in the nucleic acids. And the existence of such structural variation would allow for the possibility that, like proteins, nucleic acid molecules might also possess some kind of biological specificity. Confirmation that this was highly likely came in 1944 when work on the pneumococcus bacterium by the clinicians Oswald Avery, MacLynn McCarty and Colin MacLeod at the Rockefeller Institute came to Astbury's attention.

2. Responses to Avery's experiments, 1944–5: nucleic acids and biological specificity

That the work of the Rockefeller team has been described by one popular undergraduate textbook as 'Avery's Bombshell' is a testament to its status in the canon of modern biology.[19] It was well established that cells of the pneumococcus bacterium could be classified as either virulent, 'smooth' (S) forms surrounded by a capsule composed largely of polysaccharides, or non-virulent, non-encapsulated 'rough' (R) forms. Research carried out by a number of different workers, during the 1920s and '30s, then showed that the addition of cellular extract from S type cells was able to convert R cells into the virulent form of the bacterium—a phenomenon which was dubbed 'transformation'.[20,21,22]

It was Oswald Avery and his fellow Rockefeller clinical scientists MacLynn McCarty and Colin MacLeod who identified this 'transforming factor' within the bacterial cellular extract as deoxyribonucleic acid.[23] Avery was famously restrained in drawing conclusions from this work—in a letter written to his brother in 1943 discussing the research prior to publication, he wrote: 'Sounds like a virus—may be a gene. But with mechanisms I am not now concerned. One step at a time and the first step is, what is the chemical nature of the transforming principle? Someone else can work out the rest'.[24] The conclusions to the 1944 paper are similarly modest, restricting the findings to pneumococcus without making any wider extrapolation. The 'nucleic acids of this type', they wrote, 'must be regarded not merely as structurally important but as functionally active in determining the biochemical activities and specific characteristics of pneumococcal cells'.[25]

[15] Levene & Bass (1931).

[16] On examining the 1931 paper by Levene and Bass, Rollin Hotchkiss, a former associate of Oswald Avery, found a table compared percentages of purine and pyrimidine bases in thymonucleic acid derived from experimental measurements in Levene's laboratory 33 years earlier with theoretically obtained values. The correlation of the experimental values with the theoretical ones was at best, only very approximate with some 17 percent of the mass unaccounted for. Hotchkiss explained this disagreement as being due to the limitations of the chemical methods that Levene would have employed but says that as a result he felt that 'we need not take the values too seriously'. Furthermore, he claims that several people working on nucleic acids in the 1940s 'all stated that we didn't feel obliged to take the tetranucleotide calculations seriously'. Another column in the table purported to present experimentally derived values of base composition by H. Steudel in 1906, yet when Hotchkiss examined this original paper, these figures turned out to have been only calculated from theory 'for an arbitrary tetranucleotide'. (Judson (1980, p. 406; 1996, p. 13)).

[17] Astbury & Bell (1938b, p. 113).

[18] Judson (1996, p. 583).

[19] Watson, Hopkins, Roberts, Steitz, & Weiner (1987, p. 69).

[20] Griffith (1928).

[21] Dawson and Sia (1931a,b).

[22] Alloway (1932).

[23] Avery, MacLeod, & McCarty (1944).

[24] Avery (1943) cited in Dubos (1976, p. 219).

[25] Avery et al. (1944, p. 155.)

The Avery, MacLeod and McCarty paper prompted several attempts at replication of the experiments in other bacterial systems.[26] In New York City, Hattie Alexander, a paediatrician at the Babies' Hospital, successfully demonstrated transformation in *Haemophilus influenzae*; and in France, Andre Boivin attempted to reproduce transformation in *E. coli*.[27] The paper was the subject of discussion at a number of meetings held in the United States during 1945–1947, such as the Cold Spring Harbor Symposium of 1946 on 'Heredity and Variation in Micro-organisms', which was attended by Avery.[28] Despite later claims that the nucleoprotein model of the gene kept British scientists 'blissfully unaware' of the new findings, at least two scientists in the UK were indeed aware of Avery's work.[29]

The first of these was the Nottingham-based chemist J.M. Gulland, who, in an exhaustive 1945 study of the physico-chemical properties of nucleic acids and nucleoproteins, drew the following conclusion from Avery's work:

> It is possible, as the authors suggest, that the biological activity of the material is not an inherent property of the nucleic acid but is due to minute amounts of some other substance so intimately associated with it as to escape detection. If, however, as the evidence strongly suggests, the transforming principle is a sodium salt of a desoxypentose nucleic acid, this type of polynucleotide must be regarded not merely as structurally important but as functionally active in determining the biochemical activities and specific characteristics of pneumococcal cells. This would appear to be the first occasion on which specific transformation has been experimentally induced *in vitro* by a chemically defined substance, and its implications are of the greatest importance in the fields of genetics, virology and cancer research.[30]

The second British scientist to recognise the profound significance of Avery's work was Astbury and his connection to the pneumococcus bacterium was through botany. Thanks to a collaboration with his colleague R.D. Preston in the Department of Botany at Leeds, Astbury had from 1937 onward applied his X-ray methods to studying the polysaccharide molecules found on the surface of the cell wall in green algae such as *Valonia* and *Cladophora*.[31] An entry from a travel diary written during a lecture tour of the United States in 1937 shows however that his interest in cell surface polysaccharides extended beyond algae to bacteria, and in particular to pneumococcus:-

> Then talked about possible orientation in the polysaccharide capsule of pneumococcus. Sketched out plan of campaign with Goebel (c.f. Valonia). Introduced to polysaccharide assistant, Dr. R. Hotchkiss & then to the immunological head, Dr. O.T. Avery. Discussed problem with him too. Saw fibrous polysaccharides from pneumococci. Goebel will send samples and also dead cocci for X-rays.
>
> Most exciting![32]

At first sight, the diversity of Astbury's studies in the 1930s and 40s, ranging from hair keratin to *Valonia* and pneumococcal cell surface polysaccharides, can look undisciplined. But a letter that he wrote in October 1944 to F.B. Hanson, assistant director in the Natural Sciences Division at the Rockefeller Institute, reveals the unifying theme. The polysaccharides found on the surface of Valonia and pneumococcus were, like proteins, yet another example of how biological specificity could be accounted for in terms of three-dimensional molecular conformation:-

> A very exciting thing (to me, at least) happened the other day. I saw in a book an electron microscope photo of a pneumococcus, and—what do you think?—it seems to confirm the very thing I had been writing in the D'Arcy Thompson Essay, that I discussed with Dr. Weaver and people at the Rockefeller Institute when I visited the States in 1937. At that time I was all 'hotted up' about the beautiful crossed meridian and logarithmic spiral arrangements of the cellulose chain-molecules that we had just discovered and worked out in the wall of the alga Valonia ventricosa, and I conceived the idea that the *specificity of the polysaccharide capsule of the pneumococcus might rest not on chemistry alone but also on the geometrical arrangement of the chain-molecules constituting the capsule*—that, in other words, the structure of the capsule might be like that of the Valonia wall in miniature. I talked about this to quite a number of people in the States (including, as I say, Dr. Weaver), but of course it was extremely difficult to do anything about it then. Now, unless my eyes deceive me, this electron microscope photo is actually confirming the idea after all these years. There is undoubtedly some sort of crossed spiral arrangement wound round the 'bug', and I am dying to know more . . . This may be all hot air, in which case I shall apologise later for working you up unnecessarily; but if it is not, then it means something big, a new co-ordination of the activities of the proteins and the polysaccharides in one grand leap from an alga to a coccus.[33] (Emphasis added)

Through his interest in cell surface polysaccharides, Astbury came into contact with the biochemist W.T.J. Morgan, who was working at the Lister Institute of Preventative Medicine in London.[34] In June 1944, Morgan had published a paper in *Nature* which summarised Avery's identification of the transforming factor as nucleic acid.[35] Shortly afterwards, in a paper contributed to a collection of essays in honour of the biologist D'Arcy Thompson (mentioned in the letter quoted above), Astbury discussed Avery's latest work with great excitement and described the phenomenon of transformation in pneumococcus as 'controlled mutation'—exactly the same phrase that Morgan had used in his paper.[36] The fact that he cited Morgan's paper rather than the original paper by Avery suggests that Astbury became aware of Avery's latest findings only through contact with Morgan. Astbury was nevertheless quick to acknowledge the signif-

[26] For some time it was claimed that Avery's work was neglected or not appreciated on the grounds that it was published in a medical journal which non-clinical scientists were not likely to read (Stent, 1972; Wyatt, 1972,1975). Yet the work by Alexander and Boivin described in the main text, together with the discussion of Avery's work at scientific meetings suggest that, in certain sections of the scientific community at least, the significance of Avery's work was indeed acknowledged. (Judson (1980, pp. 382–384), Olby (1994, p. 202)).

[27] Alexander and Leidy (1951a,b), Boivin (1947).

[28] Olby (1994, pp. 202, 203).

[29] Olby (1994, p. 204).

[30] Gulland, Barker, & Jordan (1945).

[31] Astbury & Preston (1940), Preston & Astbury (1937).

[32] Astbury (1937, p. 18).

[33] Letter from W.T. Astbury to F.B. Hanson, 19th October 1944, (Astbury papers, MS419, Special Collections, Brotherton Library, University of Leeds—hereafter referred to as 'Astbury papers')

[34] Letter from W.T. Astbury to W.T.J. Morgan, 8th August 1941; 18th July 1942; 12th Oct 1942; 16th Oct 1942. Astbury papers.

[35] Morgan (1944, p. 764).

[36] Astbury (1945a, p. 348).

icance of Avery's results. In the same letter to Hanson, he acknowledged the possibility that some degree of biological specificity might reside in the nucleic acids alone:

> In this connection I was terribly thrilled to read of Avery's identification of the factor that predisposes the protein core of the pneumococcus to build its specific polysaccharide capsule (and ever after its own supply of factor too!). This is one of the most remarkable discoveries of our time and that the factor should turn out to be a bare thymonucleate after all touches me very closely for just before the war we did quite a lot of X-ray work on sodium thymonucleate and the nucleic acids in general. Indeed, the way things are going now all at once with regard to the plan of viruses, genes and cancer in the process of reproduction and growth is so exciting that it makes me wish I had a thousand hands and labs with which to get down to the problem of proteins and nucleic acids. Jointly those hold the physico-chemical secret of life, and quite apart from the war, we are living in a heroic age, if only more people could see it.[37]

Keen to become involved with this work, Astbury wrote to Avery in January 1945. Although extracts from this letter have been published by Olby to illustrate Astbury's engagement in biological matters generally, the letter bears testimony to something more precise: his interest in the possibility that nucleic acids might be capable of biological specificity. It is worth quoting from the beginning of the letter in full:

Dear Professor Avery

> I do not know whether you will remember me, but I had the pleasure of having a little talk with you about the pneumococcus and things when I was lecturing in the States in 1937. I have recently been extremely thrilled by your identification of the factor that can transform the rough variant of the pneumococcus into the smooth specific form of another type and I am writing to ask if you could possibly let me have some for X-ray examination. You may know that I have done a fair amount of X-ray work on the structure of the nucleic acids, though on account of the war, some of it is unfortunately not yet published, and in particular I have been able to obtain quite a lot of information from my photographs of highly polymerised sodium thymonucleate. I note that you identify your factor as being probably this kind of thing, and I think you will agree that it has now become a matter of considerable urgency to get down much more thoroughly to the *question of the specificity of the nucleic acids*. If I could get some decent X-ray photographs of your preparation too, it might turn out helpful and I should be very grateful indeed if you could supply the stuff . . . (Emphasis added)

And further on in the letter:

. . . I do hope you can let me have this stuff, with all relevant instructions. It seems to me that there is a wonderful chance here to make an important step forward.[38]

The letter shows just how important Astbury deemed the nucleic acids to be in the transmission of biological traits. Following the publication of Avery's 1944 paper, several critics, such as the biochemist Alfred Mirsky, had voiced objections. Perhaps Avery's preparation of thymonucleic acid from pneumococcus contained trace amounts of contaminant protein that was acting as the true carrier of the S/R trait? Advocates of such a protein-based gene model continued to voice criticisms even after Watson and Crick had published their 1953 paper on the structure of DNA.[39] But Astbury was not among the sceptics. Despite having proposed a model of protein/nucleic acid interactions in the late 1930s in which the nucleic acid strand acted as little more than structural support for the extended polypeptide chain, he was open to the possibility that nucleic acids might be capable of transmitting biological traits independently of proteins. Writing to F.B.Hanson in July 1945, Astbury clearly felt that Avery's experiment had made the problem of understanding nucleic acid specificity newly tractable:

> In a way, as I say, the whole thing has come to focus in the pneumococcus—the protein core, the thymonucleic acid transforming factor just discovered by Avery and his people and the resulting polysaccharide sheath—there we have the whole thing in a micro-nutshell, and from there I hope it will one day be possible to extrapolate even to the beautiful geometry of the wall of Valonia that I told you about.[40]

Needless to say, the mechanism by which nucleic acids might transmit biological traits was far from clear, to Astbury as to everyone else. But the letter to Avery shows that Astbury by the mid-40s was beginning to extend his ideas on specificity from the proteins and cell surface polysaccharides to the nucleic acids. If the specific immunogenicity of the pneumococcal cell surface polysaccharides was dictated by the particular spatial geometry of their polymer chains, might not the specific effects of nucleic acids also reside in their structural conformation? Astbury's closing request for a sample of material suggests that, by submitting Avery's nucleic acids to X-ray analysis, he hoped to determine whether their three-dimensional configuration exhibited structural variation comparable with that seen in the proteins and cell surface polysaccharides. If this proved to be the case then it might explain how nucleic acids, despite being composed of only four different nucleotides, could be the carriers of biological information.

3. Postwar X-ray crystallographic studies: the paradox of nucleic acids

The identification of the transforming factor in pneumococcus as nucleic acid galvanised Astbury's conviction—eloquently expressed in the recently coined term 'molecular biology'—that biological problems were ripe for analysis at the molecular level by physical methods such as X-ray crystallography. As World War II came to an end and scientists across Europe turned their minds back to research, he became determined to establish Leeds as a national centre at the vanguard of this new enterprise. Although he received official approval for his plans for a new department, certain members of the University Senate objected to 'Molecular Biology' as a departmental name on the grounds that Astbury was not a biologist by training.[41] Although Astbury finally settled for the title 'Biomolecular Structure' with some reluctance, he was far less concerned with what to call his vision of this new discipline-unifying science than to actually launch it, as is evident from the following letter to Sir Edward Mellanby at the Medical Research Council in December 1945:-

[37] Letter from W.T. Astbury to F.B. Hanson, 19th October 1944, Astbury papers.
[38] Letter from W.T. Astbury to O.T.Avery, 18th January 1945, Astbury papers.
[39] Hotchkiss (1955).
[40] Letter from W.T. Astbury to F.B.Hanson, 17th July 1945, Astbury papers.
[41] Astbury was not impressed at the choice of 'Biomolecular Structure' for the name of the new department. In a letter to Weaver, he wrote:- 'I must confess that I am rather proud that you are in the process of adopting the phrase 'molecular biology' which I believe I was the first to coin. And I am still sad that I could not get the people at Leeds to accept this name for my new department, of course, you know how it is at a University: every member of the Senate had some queer objection to my suggestion (and naturally the biologists would not grant that I was in any way a biologist!) and the result was that rather ridiculous mouthful 'Biomolecular structure'. But how simple and expressive of everything that we want to do is the name 'molecular biology'. (Astbury to Weaver, 11th Jan 1948, Astbury papers).

> Believe me, Sir Edward, for years now I have had this dream of bringing physics and chemistry into closer relation to the needs of biology, and professor or no professor, I do want to establish this new venture on durable lines—call it 'biomolecular structure' or what you will, but you know well what I mean. The time is ripe, and every day it becomes clearer that there is a real hunger among biologists for fundamental molecular knowledge. I want to help to meet this demand, and to break down the barriers once and for all; and I ask you to help me in bringing this about. This is the first time that such a Chair as Biomolecular Structure has been instituted in our own country, and I do so want to make it a real thing and the forerunner of others of the kind.[42]

But however impressive Astbury's passion for molecular biology was, it proved insufficient to win the support of the Medical Research Council. In 1946 his application for funding to establish his centre in Leeds was rejected in favour of the physicist J.T. Randall's biophysics unit at King's College, London. The grounds for this decision are unclear, but Astbury felt that his work had been deemed to be too fundamental and of insufficient practical medical application.[43]

Despite this setback, his work on nucleic acids continued. In 1947 a research assistant in Astbury's lab, Mansell Davies, took fresh X-ray photographs of thymonucleic acid, but was disappointed to find that they revealed none of the expected new structural features of the molecule. Something else, however, was by now becoming apparent from the X-ray data: the DNA molecule must contain a regular repeating structural pattern. Later that year, Astbury addressed the nature of this structural repeat in a paper presented at a meeting of the Society for Experimental Biology in Cambridge. A range of evidence suggested that the repeat was always some multiple of four nucleotides:

> What is clear . . . is this, that the pattern repeats along the axis of the molecule at a distance corresponding to the thickness of eight nucleotides or a multiple of eight nucleotides—most probably eight or sixteen nucleotides. The least possible value of the fibre period is about 27 A., which would make the effective average thickness of a nucleotide about 3.4A. The important point here has to do with the tetranucleotide constitution of the molecule, and in this connexion I wish to leave no doubt as to just what the X-ray diagram is so far telling us. It says simply that the arrangement in space is repeated along the fibre axis every eight (or sixteen) nucleotides. It says nothing yet, without very much more investigation, about the nature of the sequence, which may be determined by either chemical or geometrical considerations, or a combination of both. It hardly seems likely, though, that the fact that the intramolecular pattern is found to be based on a multiple of four nucleotides is unrelated to the conclusion that has been drawn from chemical data that the molecule is composed of four different kinds of nucleotides in equal proportions . . . for the moment we must content ourselves with the statement that present X-ray evidence indicates that probably the bulk of a Na thymonucleate fibre is constructed from molecules built to a regular pattern, geometrical or chemical or both, based on a sequence of nucleotides that is a multiple of four.[44]

In the light of the considerations outlined here and the remarks made in the earlier correspondence with Avery, we can reconstruct the nature of the problem that nucleic acids posed for Astbury as follows. If, as was believed at the time, the nucleotide bases occur in equal proportions and are arranged in blocks of four repeats, one might expect this uniformity to be reflected in the spatial geometry of the nucleic acid molecule and therefore detectable by X-ray analysis. Such a regularity in the three-dimensional structure of the nucleic acid molecule was indeed exactly what the data showed. Yet, as had been made clear by the physicist Erwin Schrodinger in his 1944 book *What is Life*, a macromolecule that was structurally uniform could hardly encompass the kind of variation needed to confer biological specificity.[45] Nucleic acids therefore presented a paradox; for while Avery's work in pneumococcus had clearly shown that they could confer biological specificity, Astbury's X-ray data revealed only a structurally uniform molecule.

For some later commentators, Astbury in his Cambridge paper had taken a 'giant step backwards into a monotonous repetition of the four nucleotides,' and so down an intellectual blind alley.[46] Closer reading of the paper, however, reveals that Astbury had not ruled out the possibility that—in line with the views surveyed in the previous section—the nucleic acid molecule might be capable of conferring biological specificity. Once again he allowed that, as was the case with other polymeric molecules, the bulk of the molecule might possess a high degree of structural uniformity and yet could still contain regions in which the molecular geometry was sufficiently irregular to confer specificity. Stressing both the uniformity and the possibility of biologically significant variation, Astbury put the case as follows:

> It seems improbable . . . to judge by the degree of perfection in the X-ray fibre diagram, that these four different kinds of nucleotides are distributed simply at random; rather must they follow one another in some definite order—at least, in more crystalline regions of the structure that give rise to the regular diffraction pattern. It is necessary to make this proviso, because in high-polymeric aggregates there is always the possibility that there are long portions of chains (or columns in this case) of sufficient regularity to build up crystallographically more perfect regions, *while at the same time there occurs every so often some chemical peculiarity that might indeed confer specificity on a structure* that is otherwise designed to perform some more standard function.'[47] (emphasis added)

It is conventionally thought that the work of the biochemist Erwin Chargaff dealt a death blow to the tetranucleotide hypothesis with two papers published in 1949 and 1950. Inspired by Avery's identification of the transforming factor in pneumococcus, Chargaff had demonstrated that not only were the proportions of the four nucleotides not equal, but that the proportions of the four individ-

[42] Astbury to E. Mellanby, 8th December 1945, Astbury papers.

[43] Astbury seemed to think that he had been rejected by the MRC on the grounds that his work had insufficient medical application, for in a letter written in 1946 to H.M. Miller at the Rockefeller Foundation he said:- 'I am rather between the devil and the deep sea—biology and industry (I will leave it to you to argue out which is which)—though I had hoped ultimately to find support definitely from medical funds, e.g., the Medical Research Council. However, it appears now that this is not going to work—I am too fundamental, or molecular, or something, to justify the expenditure of medical money on me—and I am now driven to scout around desperately once more for help, and something more permanent this time, too, so that I can at least have a few years' peaceful research free from these exhausting financial worries'. (Astbury to H.M. Miller, 23rd March 1946, Astbury papers). Other sources however have suggested that he was rejected because his research proposal placed too much emphasis on the study of artificial fibres (Olby, 1994, p. 327).

[44] Astbury (1947, pp. 67–68).

[45] Schrodinger (1944).

[46] Judson (1996, p. 93), Olby (1994, p. 324).

[47] Astbury (1947, p. 68).

ual bases varied between different species.[48] He concluded that the nucleotide sequence of a DNA molecule varied according to species, confirming that DNA must somehow be capable of a biologically specific effect. But, as we have seen, the tetranucleotide hypothesis as Astbury conceived it was a more sophisticated construction than usually credited. Far from seeing in Chargaff's work a challenge to his own, Astbury drew support from it. In 1951, Astbury wrote to Chargaff requesting some samples of DNA, for, as Astbury explained, the species-specific variation that Chargaff reported might well manifest itself as irregularities at the level of three-dimensional structure detectable by X-ray analysis:

> What about the specimens of very pure and highly polymerised nucleic acids which you kindly offered to send me when we had our pleasant little talk in your lab last summer. I should very much welcome the opportunity of seeing what can be found out from them by X-rays, especially since I have been re-reading your communications to Nature of May 13 1950. The differences in purine and pyrimidine composition that you report should be clearly demonstrable in X-ray diagrams if only we can have preparations that can be highly oriented enough.[49]

It seems likely that Chargaff sent the requested material, for in May 1951, Astbury's former photographic technician Elwyn Beighton took a number of photographs of B-form DNA (Fig. 1b). Several of these images share a striking feature: a pattern of spots in the centre that form a distinctive black cross—exactly the feature which, two years later, would ignite James Watson's enthusiasm.

4. Postwar theoretical innovations: towards a new vision of biological specificity

Why then did Astbury overlook what was so immediately obvious to Watson two years later? On Olby's account, Astbury was hampered by his vision of the gene as a nucleoprotein, the implication being that such a model of the gene must preclude any significant role for the nucleic acids. Yet it is far from obvious why this should have been the case. The term 'nucleoprotein' was used in 1941 by the cytologist Jack Schultz to describe the complexes of nucleic acids and proteins found in the chromosomes and cytoplasm. Schultz argued that these nucleoprotein complexes possessed all the necessary properties required by a gene.[50] Whilst aware that proteins were highly likely to be carriers of genetic specificity, Schultz did not however rule out the possibility that the nucleic acids might also carry such specificity.[51] Moreover, even in 1938 when Astbury and Bell had presented their model structure of DNA based on Bell's X-ray studies, the possibility that rotation of hydrogen and hydroxyl groups might endow a nucleic acid chain with sufficient structural variation to confer some degree of biological specificity had been entertained.[52] A similar idea was also echoed in 1947 when Kurt Stern proposed a nucleoprotein model of the gene in which the genetic specificity was a direct result of structural variation in a single strand of nucleic acid.[53] In Stern's model, pairs of hydrogen-bonded nucleotides projected from opposite sides of the nucleic acid chain. The immense number of permutations that this arrangement could generate was easily sufficient to generate the kind of structural variation required for biological specificity. Crucial to this model, however, was the role of flanking polypeptide chains which kept the alternating nucleotide pairs locked in position by hydrogen-bonding. Without the influence of these polypeptide chains, the nucleotides could freely rotate around the axis of the phosphate backbone and the alternating pattern would be lost. Avery's discovery that a free nucleic acid alone and independent of proteins was sufficient to confer genetic specificity posed severe problems for this model. Stern's proposed structure is nevertheless significant because it demonstrates that a nucleoprotein concept did not *ipso facto* deny a role to the nucleic acids in conferring biological specificity.

The Stern model is also significant because it further illustrates that by the late 1940s, the notion of biological specificity as a function of variation at the level of the three-dimensional structure of macromolecules was widespread. By the mid-1950s, however, a more profound vision of how biological specificity might be determined had begun to emerge from the work of Fred Sanger on bovine insulin. Chemical analyses had shown bovine insulin to be composed of particular amino acids occurring in certain proportions. Sanger's key insight was to show that in each and every polypeptide chain of bovine insulin, these amino acids were arranged in a *specific linear order*.[54] Moreover, it was this specific order of amino acids which dictated the particular three-dimensional structure of the resulting polypeptide chain. The subsequent discovery that this linear order of amino acids is in turn encoded by a specific sequence of nucleotides in a particular region of nucleic acid established a direct and intimate relationship between the three-dimensional structure of proteins and the linear sequence of nucleic acids.

Horace Freeland Judson has argued that it was the establishment of this relationship between one-dimensional sequence and three-dimensional structure resulting from Sanger's work, rather than a shift from a protein to a nucleic acid-based model of the gene, that was the key change in the making of molecular biology.[55] With the realisation that biological specificity no longer had to be manifest solely in gross three-dimensional structural variation it now became possible to envisage how even a structurally monotonous molecule such as DNA might confer biological specificity—through variation at the level of sequence. Although this conceptual development emerged after Watson and Crick's elucidation of the double helix, it is nonetheless of value in this discussion for it throws into sharp relief the particular limitations of Astbury's thinking, according to which the central theme of molecular biology was always confined to the three-dimensional structure of biological macromolecules. As he wrote in 1952:

> It [molecular biology] is concerned particularly with the *forms* of biological molecules and with the evolution, exploitation and ramification of these forms in the ascent to higher levels of organization. Molecular biology is predominantly three-dimensional and structural—which does not mean, however, that it is merely a refinement of morphology. It must at the same time enquire into genesis and function.[56]

Let us return now to Beighton's X-ray pictures. If these pictures were not outright disappointing to Astbury, as Davies has suggested, then they were likely at least to have been highly frustrating.[57] Avery's work had convinced Astbury that nucleic acids were

[48] Chargaff, Vischer, Doniger, Green, & Misani (1949), Chargaff, Zamenhof, & Green (1950).
[49] Astbury to E. Chargaff , 14th March 1951, Astbury papers.
[50] Schultz (1941).
[51] ibid, p. 56.
[52] Mudd, S. in Astbury and Bell (1938b, p. 118).
[53] Stern (1947).
[54] Judson (1980, p. 397; 1996, pp. 88–89).
[55] Judson (1980, pp. 400–402, 419; 1996, pp. 185–188).
[56] Astbury (1952) cited in Stent (1968, p. 390).
[57] Davies (1990).

indeed capable of conferring specific biological traits. His own studies on proteins and cell surface polysaccharides, however, suggested that biological specificity must be determined by variation in the three-dimensional structure of these macromolecules. Yet, far from offering evidence of such similar structural irregularities in nucleic acids, Beighton's photographs showed exactly the opposite—a macromolecule whose three-dimensional conformation was distinguished not by variation but by a regular repeating pattern. DNA, it seemed, was an enigma that would not yield to X-ray analysis; for while the molecule undoubtedly possessed specificity, it seemed to defy the prerequisite property as defined by Schrödinger, of being structurally nonmonotonous.

5. Conclusion

Generations of molecular biologists who have grown up reading *The Double Helix* may very well share the surprise of Astbury's former colleague Mansell Davies that he did not 'grasp the helical structure' from Beighton's photographs.[58] Other commentators have proposed that, as a result of Crick's earlier work on helical structures in synthetic polypeptides, he and Watson were far more attuned than Astbury to recognising a helical structure in DNA.[59] Implicit in both cases, is an assumption that recognition of a helical structure is synonymous with understanding the mechanism by which DNA replicates. Davies' surprise therefore raises an intriguing and illuminating counterfactual: what if Astbury *had* recognised the helical structure evident in Beighton's photographs? Would recognition of the helix have guaranteed an understanding of the mechanism of gene action itself for Astbury, as it did for Watson and Crick?

From Franklin's photograph, Watson and Crick deduced the helical structure of the DNA molecule and in combination with density measurements, were then able to calculate that this helix must be comprised of two separate nucleic acid chains. The problem which then arose was to explain how these two separate nucleic acid chains could come together to form a stable double helical structure, for in both purine and pyrimidine bases the key groups of atoms involved in hydrogen bonding could adopt either one of two possible forms (termed 'tautomers'—see Fig. 3a), and this duality seemed to preclude a stable pattern of hydrogen bonding between the two nucleic acid chains. On this issue, Crick acknowledged that the input of the chemist Jerry Donohue, who was working in Cambridge at that time, was crucial. Donohue pointed out that in both nucleic acid chains of the DNA molecule, each purine and pyrimidine base was highly likely to exist only in one of the two possible tautomeric forms, thus enabling a stable complementary pattern of hydrogen bonds to be formed between bases on opposite chains (Fig. 3b).[60] That this complementary base-pairing might be fundamental to the mechanism of replication of the DNA molecule and thus the transmission of hereditary characteristics is noted in the famously modest closing remarks to the first of their two papers published in 1953: 'It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material.'[61]

Once they had persuaded themselves that Franklin's photograph suggested a helical structure, Watson and Crick were, with sufficient knowledge of nucleotide chemistry, able to explain one of the most fundamental properties of the gene—its capability to self-replicate. Might a similar route have been available to Astbury had he also been similarly persuaded that Beighton's photographs suggested a helix? Given his conviction that biological specificity must reside in gross three dimensional structural variation it seems highly unlikely. A correct interpretation of the striking cross pattern at the centre of Beighton's photographs as resulting from a helix would merely have confirmed that the conformation of the DNA molecule was stubbornly monotonous whilst compounding the enigma as to how such a molecule could produce the kind of effects reported by Avery. Furthermore, even if Astbury had deduced a helical structure from Beighton's photographs, it is highly unlikely that he could have realised its true significance without the additional crucial knowledge of nucleotide chemistry that Donohue provided to Watson and Crick. Rather than cause his jaw to drop and his pulse to race, as would happen for Watson, Beighton's photographs would be for Astbury a stubborn curiousity of macromolecular aesthetics, if not an outright disappointment.

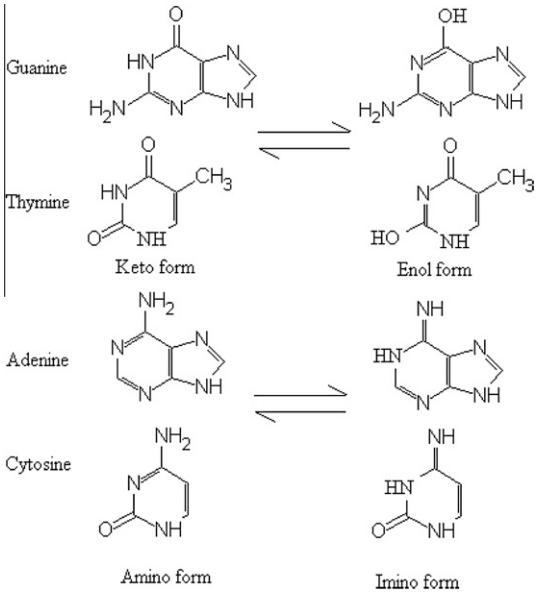

Fig. 3a. Diagram showing the tautomeric forms of the four nucleotides found in DNA. Guanine and Thymine can exist in either keto or enol forms, whilst Cytosine and Adenine can exist in either amino or imino forms.

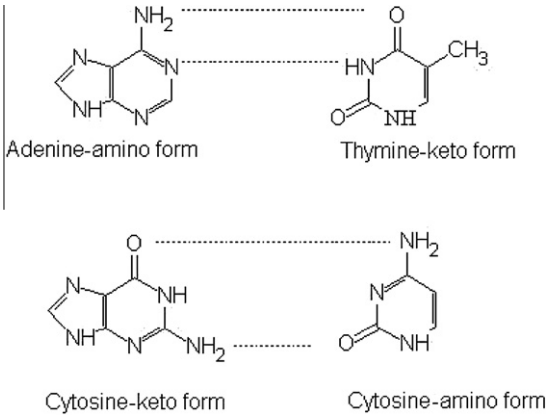

Fig. 3b. Diagrammatic representation of how the amino and keto forms of adenine/thymine and cytosine/guanine facilitate base-pairing through hydrogen bonding (hydrogen bonds are indicated by dotted lines).

[58] ibid, p. 614.
[59] Prof. A.C.T. North in Davies (1990), Cochran & Crick (1952), Cochran, Crick, & Vand (1952)
[60] Judson (1980, pp. 393–394; 1996, p. 156).
[61] Watson and Crick (1953a,b).

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