CHAPTER THIRTEEN

Support for Avery

> Recent investigations of the role of nucleic acids in biology have verified the opinion that they are comparable in importance to the proteins, especially with respect to the problem of the structure of the gene. The work of Avery on the relation of nucleic acids to the change in type of pneumococci provides a further illustration of the fundamental significance of these substances.
>
> (Beadle, Pauling and Sturtevant, 1946, 30)

> Here surely is a change to which, if we were dealing with higher organisms, we should accord the status of a genetic variation; and the substance inducing it—the gene in solution, one is tempted to call it—appears to be a nucleic acid of the desoxyribose type. Whatever it be, it is something which should be capable of complete description in terms of structural chemistry.
>
> It has been a matter for rejoicing to his many admirers, friends and followers in many countries that Avery, a veteran now among investigators, should thus, on the eve of his retirement, have attained this new peak of discovery—a fitting climax to a devoted career of such wide influence on the progress of science.
>
> (Sir Henry Dale, 1946, 128)

> None of the experiments or facts, from the very beautiful biochemical research on transforming principle to the possibly equally informative work of cytologists and geneticists, leads directly and unambiguously to the conclusion that transforming material or genes are nucleic acids, or largely composed of nucleic acids. I would appreciate learning whether or not the decision, so widespread today, that nucleic acid is a transforming principle has in fact been decided by an unequivocal experiment, or whether it is no more than a voted agreement at the present time.
>
> (Cooper, 1955, 19–20)

When a discovery is made that calls in question an established paradigm like the Protein Version of the Central Dogma one might expect the community of scientists directly involved to reject its claims and to fight a rearguard action against it on the grounds that the evidence was inadequate and could not bear an interpretation in harmony with established thought. One would then witness the familiar sequence of neglect, rediscovery and final recognition. Although it is possible to find striking examples of individuals who resisted the implications of Avery's work (Cooper, 1955; Sevag, 1952) this was far from being the only reaction to the discovery of the chemical identity of the transforming principle. This discovery was not neglected, not rejected, and not rediscovered. The Kuhnian blindness which we observed in the work on TMV in Chapter 10 was not a general feature of the discussions of Avery's work. In this and the subsequent chapter we shall explore the several

ways in which Avery's evidence was made more convincing and ways in which the implications of his discovery were followed up.

Strengthening the Evidence

In 1943 the Rockefeller group had used the reaction with appropriate anti-serum as a sensitive test (1:50 000) for the presence of protein in the transforming principle. This was far more sensitive than the histochemical and analytic (N/P ratio) evidence to which Mirsky objected. But one could still assert that during extraction and purification protein in the transforming principle was altered in such a way as to prevent it from reacting with anti-serum.

MacLeod had left the Rockefeller in 1941 to take the chair of medicine at New York University's College of Medicine. There, with Austrian, he continued his study of transformation in which he demonstrated the transfer not of just one hereditary character but of three, each of which behaved independently of the others. Directed mutation, therefore, seemed not to be the mechanism behind transformation and they concluded that there must exist a "multiplicity" of DNA molecules, each "specificity" being determined by a different one (Austrian and MacLeod, 1948, 458).

Avery, though he officially retired in 1943, continued to work at the Rockefeller for several years, and collaborated with McCarty in devising an improved procedure for extracting the transforming principle. This gave five times the yield of the 1943 technique and could be used on Types II and VI as well as on Type III (McCarty and Avery, 1946b). The pneumococcal cells were allowed to autolyse, but in the presence of citrate. McCarty had discovered the dependence of DNase upon magnesium ions (McCarty, 1946a). Citrate removed these and thus prevented depolymerization of DNA. McCarty himself had been trying since 1943 to strengthen the evidence for the identity of the transforming principle by purifying DNase. This had been available only as a crude extract of intestinal mucosa in 1943. By 1946 he was able to demonstrate activity of DNase at very low concentrations, ten thousand times weaker than the concentration at which proteolytic activity could be demonstrated! The biochemist, Rollin Hotchkiss, who had come to the Rockefeller in 1935 to work with Walther Goebel and Charles Hoagland, took up the question of the chemical identity of the transforming principle in 1947. A year later he was able to report to a conference in Paris, base compositions for the transforming principle which differed from those for thymus nucleic acid and for a tetranucleotide. He also reported inactivation of the transforming principle by the crystalline DNase which Kunitz had recently prepared (Hotchkiss, 1949; Kunitz, 1948). Next he showed that the small quantity of amino acid that could be obtained from the transforming principle was all accountable as glycine, which could be traced to the de-

composition of adenine. This important find allowed him to conclude that the maximum contamination of the transforming DNA with protein was 0.02 per cent.

Hotchkiss also sought for other markers which could, like the power to produce a capsule, be transferred to recipient cells. If what was transferred was genetic material then markers should behave independently. In the case of penicillin resistance and capsule formation he was able to demonstrate this (Hotchkiss, 1951). Later Julius Marmur worked under Hotchkiss on a strain of pneumococcus which possessed an adaptive enzyme for utilization of the sugar, mannitol. This gave the first case of linkage (with penicillin resistance) (Hotchkiss and Marmur, 1954).

These findings allowed the Rockefeller scientists to express themselves less cautiously. When McCarty addressed a symposium of the American Chemical Society on "Biochemical and Biophysical Studies on Viruses" he concluded with the words:

> It will be observed from the foregoing discussion that while the pneumococcal transforming substance is virus-like in certain of its properties, there is some evidence inconsistent with its classification with the viruses, despite the diversity of this group of agents. However, if one accepts the validity of the view that the biological specificity of the transforming substance is the property of a desoxyribonucleic acid, the results of the present study serve to focus attention on the nucleic acid component of virus nucleoproteins. In addition to its probable role in the self-reproduction of the virus molecule, the nucleic acid moiety may carry a specificity which is a determining factor in the ultimate structure of the virus.
>
> (McCarty, 1946b)

A month later (May) McCarty gave the Eli Lilly Award lecture to the Society of American Microbiologists. By this time he felt justified in concluding "that the accumulated evidence has established beyond reasonable doubt that the active substance responsible for transformation is a specific nucleic acid of the desoxyribose type." And in the body of the lecture he called for a "reconsideration of the possible role of nucleic acids in vital phenomena . . ." (1946c, 48), in the light of the "two cardinal effects" associated with DNA, namely the induction of "predictable and heritable modifications and the self-reproduction of the active agent in transformed cells" (*Ibid.*). He went on to draw analogies between the biological properties of the transforming substance and those of genes and viruses: transmissibility, recovery in quantities far exceeding the original inoculum, and unitary behaviour. "Although the validity of these analogies may be questioned, they serve to underline the possible implications of the phenomenon of transformation in the field of genetics and in virus and cancer research" (*Ibid.*).

These were all carefully measured words, and Hotchkiss was equally careful. He shied away from such crude statements as, the gene *is* DNA, or, the transforming agent is DNA. There was always the possibility lurking in

the background that the agent was DNA-dependent but not itself composed of DNA.

> We in the Avery laboratory were concerned throughout with the possibility that traces of very active protein might account for transformation. My own respect for proteins owed very much to long hours of fascinating learning from Alfred Mirsky during the thirties. Quite on my own, then, I felt the same doubts he did: that the nitrogen–phosphorus atom ratios of nucleic acid and protein could vary only as much as the phosphorus—that DNase, purified, in fact all but discovered by McCarty out of a proteinase-rich pancreas fraction, might still have mild proteinase action. Mirsky spoke about these objections, but not very much to Avery's group or he would have learned as I did how eager they were to see the search for traces of protein continued.
>
> (Hotchkiss, 1966, 189)

And so the "ifs" and "seems probables" remained: "If this be true, it is of especial interest that these determinants are available for chemical, physical, and biological study in the form of the isolated, purified transforming desoxyribonucleates of bacteria" (Hotchkiss, 1952, 436). "These analyses seem to support the earlier inferences that the determinants being transferred in the DNA transformation are the bacterial genes themselves" (Hotchkiss, 1955b, 5). Much later Hotchkiss wrote:

> . . . people *engaged in the serious analysis* of genetic mechanism were not ready themselves to be stampeded into public generalization, or beguiled entirely by visions not necessarily prophetic. The historian can later see where more emphasis, exaggeration, exposure, boldness or cajolery, would have been "justified". But do not historians also sometimes observe the danger of the "bad guesses", the places where overemphasis or persuasiveness have given a generation viewpoints that had tediously to be unlearned?
>
> (Hotchkiss, 1972)

Confirmation from Paris

Results identical with those obtained by Avery, MacLeod and McCarty were achieved with the colon bacillus *Escherichia coli* by André Boivin and his collaborators Roger Vendrely and Yvonne Lehoult. Their work is of special interest because, in addition to numbering among the first cases of transformation outside pneumococcus, its significance was hailed by Boivin in terms which, by comparison with Avery, McCarty and Hotchkiss, were recklessly speculative.

Boivin's contact with nucleic acids went back to the late 1920s when he studied among other things the metabolism of purines and pyrimidines. In the early 30s, as professor of medical chemistry in Bucharest, he collaborated with the Mesrobeanus and the Magherus. At first he studied the nucleic acid constituents of bacteria, then turned to immunochemistry and isolated the important O antigen. 1936 saw him installed in the annex of the Pasteur Institute in Garches where work continued throughout the war. There with A. Delaunay and Miss Corre, Boivin did for the antigens of the colon bacillus what Avery and Heidelberger had done for the pneumococcus. They found:

> evidence of the extraordinary multiplicity of antigenic types among the colon bacilli, each type possessing its own polysaccharide, characterized by a special chemical constitution and by a particular serological specificity. Each type remains stable through successive cultures; like the pneumococcus types, it can undergo antigenic degradation leading from form S (smooth) to form R (rough) by losing its polysaccharide, and, like the pneumococcus types again, it has the value of a true elementary species within the immense species of *Escherichia coli*.
>
> (Boivin, 1947, 7)

In 1942, after ten months spent in captivity in Germany, Roger Vendrely returned to France and joined Boivin's group. He found Boivin anxious to establish the chemical basis of transformation which he believed must involve nucleic acids. Already in 1941 Boivin had tried a variety of *in vitro* arrangements to "discover whether, like the pneumococci, the colon bacilli might not give way, by controlled mutation, to the process of type transformation" (*Ibid.*). He had read the work of Griffith, Dawson, Sia and Alloway and in 1941 he seemed to be thinking of type transformation as a phasic development (Boivin, 1941, 799). Vendrely, as the biochemist, was put on to the extraction of the transforming substance. The donor cells were killed with chloroform and allowed to autolyse for two days at 37°C. Nucleoprotein was then precipitated from the autolysate by acetic acid. The Paris workers were then told about Avery's 1944 paper revealing the role of DNA. "Inspired by this work," said Boivin, "we too have obtained evidence of the intervention of desoxyribonucleic acid in directed mutations in bacteria. We take pleasure in acknowledging the priority of the American authors in this field" (1947, 9). All that Boivin and his colleagues had to do, it appeared, was to treat their nucleoprotein extract with pepsin at pH 2, or better, to use the Sevag-chloroform technique, to strip off the protein. At a meeting of the Académie des Sciences, in November 1945, Boivin announced his success in achieving transformation in *E. coli*. From the R form of Type S, they produced the S form of Type S_2 when cultured with a nucleic acid extract of the latter. Likewise they achieved transformation of S_2 to S_1. In December 1945 *Experientia* published these findings. The title of the paper contains the phrase "Significance for the biochemistry of heredity". The conclusion, in which the donor type is referred to as C_1 and the recipient type as C_2, translates as follows:

> It seems well established now that the bacterial cell possesses a small nucleus of thymonucleic acid immersed in a cytoplasm of ribonucleic acid. Surely the principle derived from C_1, which demonstrated its ability to impose on C_2 a new molecular constitution for its polysaccharide and a novel enzymatic equipment, results from a simple "solubilization" of the rudimentary chromosomal apparatus of C_1? The hypothesis seems likely. If it corresponds to reality, it opens altogether novel horizons, and how promising these are for the biochemistry of heredity. In particular, it is on the side of the nucleic acid and not at all on that of the protein of the nucleoprotein macromolecule constituting a gene that one must find the basis for the inductive properties belonging to the gene. That would lead one to envisage the possibility of a "primary" or more likely "secondary" structure

> able to differentiate between the various desoxyribonucleic acids within their natural state of polymerization.
>
> (Boivin, Delaunay, Vendrely and Lehoult, 1945, 335)

When Boivin attended the Cold Spring Harbor Symposium in June 1947, he gave a remarkable paper in which he related the work on bacterial transformation to Beadle and Tatum's work on biochemical genetics, described Tulasne's confirmation of Robinow's work on the bacterial nucleus (1947), and the chemical mechanism involved (Vendrely and Lipardy, 1946), and gave Tulasne's and Vendrely's cytochemical evidence, using RNase and DNase, for the localization of RNA in the bacterial cytoplasm and DNA in the nucleus of *E. coli* (1947).

When we look back over the mass of literature in the 1940s, it seems scarcely possible that André Boivin could have so accurately predicted the structure which the nascent subject of molecular genetics was to take. Consider the following statements:

> We may, at the most, catch a glimpse of a series of catalytic actions which set out from primary directing centres (the desoxyribonucleic genes) proceed through secondary directing centres (the ribonucleic microsomes–plasma–genes) and thence through tertiary directing centres (the enzymes), to determine finally the nature of the metabolic chains involved, and to condition by this very means, all the characters of the cell in consideration.
>
> Thus, this amazing fact of the organization of an infinite variety of cellular types and living species is reduced, *in the last analysis*, to innumerable modifications within the molecular structure of one single chemical substance, nucleic acid, substratum of heredity as well as of acquired characters. This is the "working hypothesis" quite logically suggested by our actual knowledge of the remarkable phenomenon of directed mutation in bacteria.
>
> Thus there exist in the bacterial nucleus, as in the cell nucleus of higher organisms, desoxyribonucleoprotein genes which serve as a substratum for the characters of the species. It follows that whatever happens in the phenomenon of directed mutation can hardly be interpreted otherwise than as a result of solution of the bacterial chromosome apparatus without total destruction of its functional value.
>
> In bacteria—and, in all likelihood, in higher organisms as well—each gene has as its specific constituent, not a protein but a particular desoxyribonucleic acid which, at least under certain conditions (directed mutations of bacteria), is capable of functioning *alone* as the carrier of hereditary character; therefore, in the last analysis, each gene can be traced back to a macromolecule of a special desoxyribonucleic acid. . . . This is a point of view which, in respect to the actual state of biochemistry appears to be frankly revolutionary.
>
> (Boivin, 1947, 12-13)

In the ensuing discussion, Brachet expressed surprise that Boivin's autolysates were active in transformation. Surely DNase was present and therefore the activity must have been due to some substance other than DNA. All Boivin could do was to assure Brachet that whereas colon bacilli contained a very active RNase there was no evidence of a similarly active DNase, for Vendrely had found the proportion of RNA to DNA to fall very markedly during autolysis (Vendrely, 1947). Probably informally, Boivin was asked why he had not used sodium desoxycholate, like Avery, or molar NaCl like Mirsky.

So he added a footnote to his paper saying that colon bacilli resisted both reagents so strongly that only very poor yields resulted from these extractive procedures. Hotchkiss had this to say about Boivin and his evidence from *E. coli*:

> Boivin was respected for his identification of bacterial antigens far more complex than those Avery had identified a couple of decades before. Boivin was I think also widely considered an honest scientist, optimistic and given to simplistic logic. It is fitting that he should appear in your lights as an early molecular biologist! But he lacked the quantitative sense and self-critical attitude the best molecular biologists were to show. I doubt if we will ever know whether he and his coworkers ever really achieved a DNA-caused transformation since (I am told) his strains spontaneously go through the same change. It would have been outside his realm of inquiry to consider the role of *selection* in fostering the conversions—so with Avery's prior example just before him, I think he was overpersuaded by his own scant observations.
>
> Boivin called it "fifty per cent transformation" when (literally, when pursued) he meant that transformation *occurred in* one half of the *flasks* treated with DNA under best conditions. We asked, by 1951 and before, what per cent of *treated cells* are changed? His personal magnetism and enthusiasm were great, but these things are dangerous when matters are in a qualitative stage.
>
> (Hotchkiss, 1972)

Accordingly, we find another footnote in Boivin's Cold Spring Harbor paper which reads:

> Despite apparently identical experimental conditions, the transformation of R_2 into S_1 through the action of the desoxyribonucleic acid of S_1 is not regularly produced. In a dozen tubes, containing the same volume of medium and the same dosage of desoxyribonucleic acid, inoculated with the same number of bacteria, one frequently finds tubes giving rise to transformation side by side with others where no transformation occurs. The number of bacteria at the beginning and end of the culture and the concentration of the desoxyribonucleic principle do not allow an explanation on statistical grounds of the proportion of positive results obtained in the different experiments. All takes place as though a factor, still unknown, were able to facilitate or to prevent transformation.
>
> (Boivin, 1947, 8)

To make matters worse, other workers had difficulty in repeating Boivin's work, perhaps due to the difference in the competence of different strains (Ravin, 1969, 65). Had Boivin's strains 17 and 24 been available to other workers, confirmation might have resulted, but these strains "were lost when the tubes containing the parent strains were broken in a careless accident" (Vendrely, 1972). Boivin was at the time in hospital following his first serious attack of cancer, and Lederberg and Tatum, who received strains from Boivin in 1947, "never confirmed his finding. In correspondence with Tatum, Boivin admitted that these might have lost their competence in his own hands, and he stated he would try to recover others on which he could verify the transformation himself. His illness supervened" (Lederberg, 1972a).* At Columbia, where "Avery's work was very well known" (Lederberg, 1973). Ryan and Lederberg had in June 1945 tried "to emulate Avery by trans-

* Transformation has since been achieved in *E. coli* (see: Oishi and Cosloy, 1972; Wackernagel, 1973).

forming *Neurospora* mutants with DNA extracts. This was unsuccessful, and was therefore regarded as unworthy of report" (Lederberg, 1972b). It had been carried out precisely to clarify "whether 'transformation' was a typical gene transfer" (Lederberg, 1972a). Meanwhile, Boivin's work found its way into the literature as a confirmation of Avery's discovery, and Arthur Pollister, who had collaborated with Mirsky, was greatly impressed by the French work, especially that of Boivin's collaborator, Vendrely (see Chapter 14).

The Debate over Bacterial Transformation

It has been urged that the famous Avery, MacLeod, McCarty paper was not widely read because it was published in a journal normally found only in medical libraries (Wyatt, 1972). It is true that Avery made no attempt to get a short report of the work published in a widely circulated journal like *Science* or *Nature*. On the other hand news does not have to be published in order to travel! Quite apart from visits made by such scientists as Gulland (1946) and Macfarlane Burnet (1943), transformation was discussed at three unpublished symposia: The Mutation Conference, New York, January 1946. Biophysical and Biochemical Studies on Viruses, Atlantic City, April 1946. Conference with unknown title, Hershey (Penn.), October 1946.

The subject of the Cold Spring Harbor symposium of July 1946: "Heredity and Variation in Micro-organisms", had been chosen in the year Avery's paper appeared and the meeting would have been held in 1945 had not travel restrictions made it impossible. When the participants met in 1946 Avery, McCarty and Harriet Taylor were present and reported on the progress they had made in identifying the environmental factors essential to transformation. At yet another meeting in 1946—Society of American Microbiologists at Detroit—McCarty read almost the same fine paper that he had given in Atlantic City a month before. On this occasion he received the Eli Lilly Award in Bacteriology and Immunology. Nor did this flush of interest subside in 1947. The Cold Spring Harbor Symposium of June 1947 was devoted to nucleic acids and nucleoproteins. Boivin, Chargaff, Hotchkiss, Mirsky, Pollister and Harriet Taylor were present.

These meetings gave adequate opportunities for geneticists, virologists and biochemists to discuss transformation. In Europe the scene was less conducive to the publicizing of Avery's work. When the Society for Experimental Biology held a meeting on nucleic acids in Cambridge (1946), no one was invited to talk on transformation, and in his paper on bacterial nucleic acids and nucleoproteins M. Stacey succeeded in submerging his account of Avery's work in a list of what everyone else had done. Enthusiastic though he was, Stacey's own interpretation was clearly in the nucleoprotein camp (Stacey, 1947, 96).

There was one bright exception—the exciting colloquium held in Paris in 1948 by the Centre Nationale de la Recherche Scientifique (C.N.R.S.) with support from the Rockefeller Foundation. But even this meeting failed to have the wide impact which it most certainly deserved, perhaps because the proceedings were published in French in a limited number of copies of the C.N.R.S. colloquia.

This gathering had been planned by André Lwoff and Boris Ephrussi. They entitled it: "Biological Units Endowed with Genetic Continuity". "A year later", wrote Hotchkiss, "before I had realized that I almost never would find anyone who had read the symposium article, I was distressed to find that a tired abstractor for *Chemical Abstracts* had covered my own and also Ephrussi's conference papers in two short words, 'a review' " (Hotchkiss, 1966, 190). But what a grand colloquium it had been! Hotchkiss had reported his work with crystalline DNase and his quantitative chromatography of the transforming DNA. Boivin later referred to this as "the first direct argument of a chemical nature in support of the existence in nature of a multiplicity of nucleic acids" (Boivin, 1948, 1258). Harriet Taylor had described "intermediate" and "extreme" forms of pneumococci and had provided evidence for the presence of at least two functionally distinct DNAs in one and the same bacterial extract. Boivin, who by this time had moved with Vendrely to Strasbourg and had been joined by the cytochemist R. Tulasne, described their work on the localization of DNA and RNA in the bacterial cell, and their measurement of the DNA content of diploid and haploid cells.

These important contributions were summed up by André Lwoff in the following words:

> The transforming principle of pneumococcus is deprived of proteins and appears to consist exclusively of desoxyribonucleic acid. This is probably the case also for *Escherichia coli*. The importance of DNA is indicated by the fact that diploid nuclei have twice the DNA of haploid nuclei. The study of the transforming principle of pneumococcus has led to the conclusion that the purine and pyrimidine bases are not present in equimolar proportions. This gives an inkling of a possible explanation for the specificity of nucleic acids. Once the transforming principle of pneumococcus is introduced into a bacterium it confers on it permanently a given specificity. But this principle is susceptible of modification and even at the present time we know of two varieties of specific nucleic acid of type III pneumococcus. They have been compared to allelomorphic genes. In fact, they exclude each other reciprocally as if in competition for the same receptor.
>
> This fact thus throws light on the idea that the specific nucleic acids normally could and should be combined with another constituent, probably a protein.
>
> (Lwoff, 1948, 202)

The Influence of Studies in Transformation

There is no doubt whatever that the Avery paper of 1944 had a profound effect on biochemists. "These wonderful discoveries", said Mirsky, "have caused chemists to consider critically the evidence for uniformity among

nucleic acids, and the generally accepted conclusion is that the available chemical evidence does not permit us to suppose that nucleic acids do not vary" (Mirsky, 1947, 15). I fear that his criticism of the evidence for DNA as the transforming substance did incline influential geneticists like Muller to retain the nucleoprotein conception of the gene rather than to go over to the DNA conception. But within the ranks of biochemistry Mirsky's criticism may well have served to stimulate further work. We have already referred to the genetic studies by Harriet Taylor and Rollin Hotchkiss. Two further lines of research naturally suggested themselves: studies of DNA content of cells and analysis of the base constitution of DNAs from different species. In short, Avery's work on bacterial transformation was not neglected. It did lead directly to further chemical and genetic studies, the outcome of which was crucial for Watson and Crick. This is not to say that those microbiologists and histochemists who supported the new view rapidly dominated the entire scene; conservatism lingered on as seen in Kenneth Cooper's outburst of 1955. Nor was the new view influential in England, where the old school of geneticists and plant virologists complacently carried on with the nucleoprotein gene. Perhaps it was Gulland's death in 1947 which left the British scientists to all intents and purposes blissfully unaware of the new developments in nucleic acid chemistry across the Atlantic and in Paris.

The Significance of Bacterial Transformation

With the passage of time the work of Avery, MacLeod and McCarty looks, if anything, more significant than in 1958; perhaps it was the most important event in undermining the pre-eminence of the protein, the culmination of a series of achievements which established the chemical basis to enzyme action, antigenicity and finally transformation. It marked the beginning of a new era in which a search for the chemical basis of nucleic acid "specificities" was undertaken. Muller admitted that if DNA was the transforming substance as Avery, MacLeod and McCarty concluded "their finding is revolutionary" (Muller, 1947a, 22). Boivin likewise felt that in the state of biochemistry at that time the postulation of many different DNAs "appears to be frankly revolutionary" (Boivin, 1947, 12). One does not find scientists describing a discovery as "revolutionary" every day of the week. This discovery was special. It demanded a re-examination of the Protein Version of the Central Dogma and of the tetranucleotide hypothesis. It suggested there must be hidden in the molecules of nucleic acids chemical specificities as rich as those of proteins. The debate over bacterial transformation therefore marks as Kuhnian a revolution as did the debate over macromolecules.

When we enquire into the reception Avery was given in the Rockefeller itself we find that on the surface at least there was enthusiasm. P. A. Levene, who died in 1940, was of course aware of the work on transformation in its

earlier stages. "He was sceptical about the possible role of DNA in the transformation reactions and when Dr. Avery and I [MacLeod] described the system to him . . .—what the results were—and the properties we then knew about the active material, he was highly sceptical that it could be DNA" (MacLeod, 1968).

By 1943, when Avery read the great paper at the formal after-tea meeting in the Rockefeller, "there was next to no discussion . . . because it was a standing ovation afterwards. There was obvious recognition and a terrifically warm reception. Nobody mentioned any objection" (McCarty, 1968). The story that Avery was vehemently attacked in a discussion following the lecture and as a result dared not show his face in the Rockefeller for several weeks thereafter is clearly untrue.

There was, of course, opposition from Mirsky which was expressed publicly at meetings outside the Rockefeller. We have already examined the scientific grounds for this opposition. But such opposition can rarely be considered in isolation from other less objective grounds. We have noted that all three men —Avery, MacLeod and McCarty—were trained in medicine, not in biochemistry. True, they differed from men like Griffith, whose interests in epidemiology did not spill over into biochemistry. But medical research was messy, the systems used in experimentation were complex to the point where the results obtained from them were unreliable, and the transformation system was far from being an exception. No doubt, therefore, there was that feeling of professionalism on the part of biochemists in the Institute, like Mirsky, which predisposed them to question the contribution of "doctors", like Avery, MacLeod and McCarty, in the Institute's hospital. The same attitude exists to this day on the part of many a "pure" science department towards an "applied" science department.

Not only did the transformation story involve this conflict between biochemist and medic but in Sir Macfarlane Burnet's view it signalled a change from applied to pure research.

> Looking back I fancy that it was only in the 1930s that medical scientists began to be really interested in "pure" research . . .
>
> What swung microbiology perhaps for ever away from a primary desire to prevent and cure infectious disease to its current preoccupation with molecular biology, was probably Avery's discovery . . .
>
> (Burnet, 1968, 59)

Burnet visited Avery in 1943 and wrote home to his wife telling her that Avery:

> "has just made an extremely exciting discovery which, put rather crudely, is nothing less than the isolation of a pure gene in the form of desoxyribonucleic acid." I think that must be almost the last time I ever wrote DNA in full. Nothing since has diminished the significance or importance of Avery's work. Neither he nor I knew it at the time but in

> retrospect the discovery that DNA could transfer genetic information from one pneumococcus to another almost spelt the end of one field of scholarly investigation, medical bacteriology, and heralded the opening of the field of molecular biology which has dominated scholarly thought in biology ever since.
>
> (*Ibid.*, 81)

Parallel with this change, the introduction of new drugs like penicillin and the sulphonamides made further attempts to develop immunological aids of the sort the Rockefeller bacteriologists had been working on superfluous. Men like Hotchkiss who had started out contributing to a problem in immunochemistry found themselves drawn into the genetics of bacterial transformation.

Thus it came about that work begun by Griffith, a civil servant in the Ministry of Health, was taken up by a medical institute, and was there developed to answer the question: "On what compound does the specificity of the gene depend?" The Rockefeller's administrators, who had shown so little interest in genetics in the early days, now became very definitely committed to it.