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Supplementary data
"Data Supplement"
http://rsbm.royalsocietypublishing.org/content/suppl/2009/04/24/47.0.369.DC1

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BACKGROUND AND EARLY YEARS

Albert Neuberger was born in 1908 in the small Franconian town of Hassfurt, which is in the north of Bavaria. At the time of Albert’s birth, the Kingdom of Bavaria was a semi-autonomous state of the German Empire.

His parents were Max Neuberger and Bertha, née Hiller. His ancestors on both sides had been in the region for several generations and were small-town business people with an interest in scholarship and local affairs. They were religious Jews with a strict, somewhat Victorian, sense of moral values, who mixed freely and without any self-consciousness with their Christian neighbours.

He had a happy, secure childhood and was very close to both his parents. He described his father as being a businessman who was more interested in a variety of intellectual activities than in his business. Albert was the eldest of three children. He attended the local elementary school from the age of six, but had already been writing German and Hebrew from the age of five. At the age of nine he was sent to a secondary school in Würzburg. However, the end of World War I brought about difficult conditions in the larger towns and he was therefore taken back to Hassfurt, which was peaceful and had a good supply of food. For the next four or five years he was taught by a variety of tutors including the local Protestant pastor. He received a good grounding in Latin, Greek, Hebrew, mathematics and history, but no science. By the end of 1923 he was able to return to Würzburg to attend the Neue Gymnasium (high school). (On a visit to Würzburg in the 1990s he was shown his name on the board of honour in his old
school.) For the most part he studied classics but also had good teaching in mathematics and physics. He was not taught any chemistry or biology. He said in later life that he never regretted the time spent on Latin and Greek and that he regarded classical studies as being an excellent background for any academic study.

At the age of 18 he entered the University of Würzburg as a law student, with the intention of later following an academic career and concentrating on the history and philosophy of law. However, during his first term he began to doubt the wisdom of his choice, started to attend science lectures and became particularly interested in physiology. In the second term he transferred to the preclinical medicine course, took enthusiastically to chemistry and biochemistry, and passed with distinction in 1928. He made his clinical studies in Würzburg and Berlin, passed all his examinations with distinction and was awarded an M.D. *summa cum laude*, in 1931. This MD work also resulted in the publication of his first two scientific papers on intracellular proteolysis (1, 2)*.

During his time as a student in Berlin he devoted much of his spare time and his long vacations to working in the laboratory of Professor Peter Rona, who introduced him to the modern aspects of biochemistry. His periods in Berlin (1928–32) were a crucial time in German history. Having come from a conservative south German city he was rather shocked by the liberated social and sexual culture, but he also found the atmosphere culturally stimulating. He felt that the pre-1914 values had disappeared but had not been replaced in a satisfactory manner. This was particularly noticeable in politics, in which a situation arose of two violent extreme parties, the Nazis and the Communists, who were squeezing out the moderate political groups. He therefore feared that Germany was heading towards either a left-wing or right-wing totalitarian regime and he felt that it would be impossible to live under either.

After completion of his medical examinations, from 1931 to 1932, he did 18 months of clinical work in Frankfurt and Würzburg in the equivalent position to a house officer. Although he enjoyed clinical work, he decided to return to Rona’s laboratory in October 1932 for further laboratory experience. However, there was then a rapid deterioration in the political situation, so with Rona’s introductions he visited laboratories in Amsterdam and London. He became convinced that he would be happy to live in England but returned to Berlin without having made a final decision. In Berlin it then became obvious to him that the Nazis were going to gain power and at the end of 1932 he moved permanently to London. This was a wise decision, as on 30 January 1933 Adolf Hitler became Chancellor of Germany.

In the next six years his immediate family managed, with his help, to leave Germany. His sister, who was five years younger, had followed him to medical school in Würzburg but was expelled by the Nazis in 1934, before completion of her studies. She migrated to Palestine and became a farmer’s wife. His brother, who was 10 years younger, moved via England to the USA and became a well-known rabbi. His father had died in 1931; his mother and grandmother survived rather precariously in Würzburg until 1938, when he was able to bring them to England.

He was obviously not forgotten by the German authorities because his name appeared on a rather distinguished list of 2820 residents of the UK that was compiled by the Gestapo in 1940. These were people who were to be arrested as soon as possible after the German invasion, which was scheduled for the autumn of that year.

* Numbers in this form refer to the bibliography at the end of the text.
Albert Neuberger

CAREER

With an introduction from Professor Rona he was able to start work in the laboratory of Professor C.R. (later Sir Charles) Harington, F.R.S., at University College Hospital, London. His work on the electrochemistry of amino acids and proteins was also greatly influenced by the distinguished physical chemist Professor F.G. Donnan, F.R.S., who was at University College London. Neuberger was supported by a grant from the Academic Assistance Council, which had been founded in 1933 and was financed by a remarkable collective act of generosity of university staff to help academic refugees from Europe. He gained a PhD in 1936 and was then awarded a Beit Memorial Research Fellowship so that he could continue to work at University College Hospital Medical School. He remained there until 1939, working on the question of whether sugars were true components of 'normal' proteins.

At the outbreak of war he was invited by Sir Frederick Gowland Hopkins, F.R.S., to join the Biochemistry Department at Cambridge. As this was one of the world centres for biomedical research he found this to be a very stimulating environment, not only for the biochemical discussions but also in the opportunities to meet historians, linguists and philosophers. He also enjoyed involvement in the teaching of biochemistry for Part II of the Cambridge Tripos.

As he had been told that he could not join the armed forces because he was in a reserved occupation, he felt under an obligation to do some work that was of direct value to the nation in time of war. After some initial research on adhesives for the Royal Air Force, he decided, after discussions with Sir Charles Martin, Director of the Lister Institute, to work on the nutritional value of the potato. He was joined in this work by a newly graduated student called Fred Sanger (subsequently a double Nobel laureate; F.R.S. 1954), who became his first PhD student. Apart from the work on potato, they both had an interest in the fundamentals of protein structure. Neuberger had an interest in insulin and they derivatized it with benzene sulphonyl chloride to confirm previous indications that phenylalanine was an amino-terminal end-group of insulin. Sanger later independently developed the use of fluorodinitrobenzene as an end-group reagent for sequencing studies. Sanger (1988) said of him:

I regard Albert as my main teacher. The most important thing he taught me, both by instruction and example, was how to do research. I shall always be grateful for his kindness and patience. He also had an extremely wide knowledge of biochemistry, which I admired and used but could never emulate.

In January 1943, at the invitation of Harington, he joined the Medical Research Council's National Institute for Medical Research (NIMR) (initially at Hampstead and later at Mill Hill), where he was in charge of the Biochemistry Division until 1954. His initial research was on protein nutrition and the requirements for amino acids in conditions of starvation, injury and burns. Later work was on amino-acid and porphyrin synthesis (see below).

Early in 1945 he went to India as consultant in nutrition to the Indian Army. To give him sufficient status with the military establishment he was appointed to the rank of Brigadier. As he remarked, rarely had promotion been so rapid, as his previous rank had been that of Lance Corporal in the Home Guard. He was there for four months, during which time he travelled very extensively and advised on many nutritional problems. He also pointed out that population growth was likely to be a major problem for the future, a viewpoint that was not generally recognized then. In fact, at that time, the medical establishment in India was concerned about a predicted decrease in population.
In 1954 he was invited to fill the newly created Chair of Chemical Pathology at St Mary's Hospital Medical School, London, where he remained for 18 years. He had decided, with his qualifications in both science and medicine, that he wished to return to a more clinical environment and he was offered a position where the teaching and administrative burdens were not too heavy. He was in overall charge of routine chemical pathology, but was able to delegate the day-to-day responsibilities to others. He enjoyed being in touch with the clinical environment but was very happy to be able to build up research groups working on porphyrins, glycoproteins and carbohydrates.

During his time at St Mary's he also accepted the request to become Principal of the Wright–Fleming Institute at St Mary's. In this post he upset some of the staff by his assessments of their work, because they were not used to being subjected to critical appraisal. He also recruited new staff of very high quality, one of whom was Rodney Porter (F.R.S. 1964), the future Nobel prizewinner. Porter was recruited from NIMR, Mill Hill, to the new Chair of Immunology in 1959 despite the objections of some members of the selection committee that a candidate without medical qualifications should not be appointed to a chair in the Wright–Fleming Institute (see Perry 1987).

On retirement he continued his research in the Biochemistry Department of the Charing Cross Hospital Medical School. During these periods he held many other important posts including the chairmanship of the Lister Institute. In addition, he had close associations with the Weizmann Institute and Hebrew University of Jerusalem.

**Research activities**

Throughout his life, Albert Neuberger showed an unusually broad interest in science and medicine. He made highly significant contributions in the areas of the chemistry and biochemistry of amino acids (especially of glycine, serine, tryptophan and hydroxyproline), nutrition (with particular regard to amino acids and proteins), porphyrin biosynthesis, the chemistry of sugars (particularly amino sugars), lysozymes, lectins and especially glycoproteins (see (55) for summary).

**Glycoproteins and lectins**

His pioneering work on glycoproteins started in 1936 (4). At that time most biochemists felt that, with the possible exception of mucins, the carbohydrate that could be detected in protein preparations was just an impurity. Neuberger felt that because many proteins gave a positive reaction in the Molisch reaction, which is specific for carbohydrate, at least some of these proteins were likely to have covalently attached sugars. He chose to investigate hen egg-white albumin because it was readily available and could be crystallized. Before chromatography had been developed, the only possible purification method was by repeated (sevenfold) crystallization until the preparation had a constant ratio of protein to carbohydrate. He then subjected the ovalbumin to exhaustive proteolytic digestion followed by acetylation and solvent extraction to remove the free amino acids from the digest. He was able to isolate a compound with a molecular mass of ca. 1200 Da. He determined its composition and found that it contained four molecules of mannose and two of N-acetylglucosamine. Its nitrogen content indicated that there was another component present with two nitrogen atoms. These experiments established that carbohydrate was attached covalently to ovalbumin and that it was present mainly as a hexasaccharide. The linking amino acid was suspected by Neuberger.
to be asparagine or glutamine, but with the techniques available at that time and also with the outbreak of war he was not able to pursue the investigation.

This problem was taken up again in the 1950s with R.D. Marshall and P.G. Johansen (25, 26), and they were able to prove with other co-workers that the linkage between the protein and carbohydrate moieties was between the amide of asparagine and the reducing carbon atom of \(N\)-acetylglucosamine (27, 32–36, 39). His group then synthesized the linkage compound, which established the structure beyond any doubt (28). This has subsequently been shown to be a conserved linkage structure in all animals, plants and protozoa.

In 1965–66, together with Robin Derek Marshall, an attempt was made to establish the particular amino-acid sequences in proteins that could lead to glycosylation. They showed that the sequence Asn–Xaa–Ser (or Asn–Xaa–Thr), where Xaa can be any amino acid except proline or cysteine, was required for the N-glycosylation of asparagine with \(N\)-acetylglucosamine (43).

His work on lectins was initiated by Nathan Sharon, who spent six months in Neuberger’s laboratory in 1971, and followed on from work in the laboratory on the carbohydrate-binding lysozymes. The work was in collaboration with Tony Allen and started on wheatgerm agglutinin. It was concluded that the lectin was a cysteine-rich protein with an extended binding site with subsites for oligosaccharides of \(N\)-acetylglucosamine resembling the lysozymes. This was the first of the chitin-binding lectins to be purified (44).

Other lectins with similar specificities from potato and related plants were shown to contain not only a cysteine-rich domain similar to wheatgerm agglutinin but also a highly glycosylated hydroxyproline-rich region and has a collagen-like polypoline II structure that is stabilized by glycosylation (45, 47–54).

Other studies were made on extensively characterizing lectins from \(Vicia\ faba\), pea and lentil. It was concluded that they differed from concanavalin A in that they strongly bound 3-\(O\)-methylhexoses, indicating that there is a strong hydrophobic interaction in the binding site (46). These observations led to structural studies by X-ray crystallography, which confirmed the general conclusions.

A urinary glycoprotein was described by Tamm & Horsfall (1950). Neuberger’s group characterized the glycoprotein and showed that it contained ca. 30% carbohydrate, was very rich in sialic acids and was produced by kidney cells in culture (40–42).

**Amino sugars**

In his work on glycoproteins he became interested in the chemistry of sugars, particularly of glucosamine and its derivatives. He prepared the methylglucosides of glucosamine and \(N\)-acetylglucosamine. The only previous work on this compound had been done by Irvine and co-workers (Irvine et al. 1911; Irvine & Hynd 1912), who had prepared the compound and had concluded that methylglucosamine did not have a normal glycosidic structure because of its unusually strong resistance to acid hydrolysis. In 1938, with Moggridge, Neuberger proposed that the compound did have a normal glycosidic linkage and that the resistance to acid hydrolysis in comparison with neutral sugars was due to an electrostatic effect from a positively charged amino group. In kinetic experiments they showed that the rate of hydrolysis of methylglucosaminide was ca. 1% of that of the uncharged methyl glucoside. In a later paper in 1940 (5) he proved by O-methylation analysis that glucosamine really was 2-amino-2-deoxyglucose and that its glycosides were pyranosides. This work was fundamental to many subsequent studies on the structure of glycoproteins.
Studies on the ionization of sugars were continued in his laboratory in the 1970s, not only of the amino group, but also of the acetamido and hydroxyl groups. Separations of sugar derivatives on ion-exchange columns were explained in terms of differential ionizations of hydroxy groups.

*Electrochemistry of amino acids and proteins*

His PhD work was concerned with the dissociation constants of amino acids, particularly glutamic acid and its esters, and he retained an active interest in this field throughout his career. This led to fundamental work on protein structure.

He studied the iodination of insulin and zein, which was affecting the phenolic residues of tyrosine and led to a shift in $pK_a$ values of about 3.5. In a paper with Harington (3) he showed that the derivatized insulin had lost almost all its biological activity and was able to demonstrate the restoration of activity by deiodination. They then studied ultraviolet spectroscopy of the proteins in native and denatured states by observing the changes with pH. This was very laborious because at that time only two spectrograms could be done on a protein in a day. They postulated that hydrogen bonds were largely responsible for the stability of native proteins. This was probably the first use of UV spectroscopy for such studies.

*Nutritional studies and amino acid metabolism*

His interest in nutrition started in 1940 as war work for his first PhD student, Fred Sanger, in which they were investigating the nutritional value of the potato proteins, which was unexpectedly high (6). This led to extensive studies on the metabolism of the essential amino acid lysine in rats (7). Later, when at the NIMR, he made a particular study of the pathology resulting from diets deficient in sulphur-containing amino acids. They concluded that the necrosis of the liver that was seen was due to a decrease in the concentration of liver glutathione (9).

He was involved in many studies of amino-acid metabolism and chemistry, including work with Arnstein on the feeding of labelled glycine and serine to rats, which established the importance of the $\beta$ carbon of serine as a methyl donor via tetrahydrofolate (20), with Elliott on the special nutritional position of threonine (14), with the Cornfords on the metabolism of tryptophan (17, 18) and with Hudson on the stereochemistry of hydroxyproline (8, 10).

At Cambridge, Neuberger had an interest in the chemical modification of particular amino acids in insulin using benzene sulphonyl chloride. Although he did not take this further, it did encourage Sanger to develop fluorodinitrobenzene independently as an end-group reagent. Sanger (1988) said of him:

> I knew him best in the 1940s when I became his first PhD student, and I have always felt grateful for all he did for me at that critical time in my career. Not only did he teach me a lot of biochemistry, but—more important still—he taught me how to do research.

*Protein metabolism*

With the availability of radioisotopes after World War II, the possibilities for metabolic turnover studies increased enormously and Neuberger was one of the first to recognize this potential. Before radioisotopes were available, the concept of turnover was not considered to be of importance by most biochemists. He said that although the turnover of proteins in organs such as the liver and kidney had been recognized, the turnover of structural proteins such as collagen had not been investigated. The work of his group at the NIMR showed that
collagen did indeed turn over by a method in which the turnover was measured not by the rate of incorporation of labelled glycine but by the rate of its disappearance from the tissues. From this they found that the rate of turnover varied considerably between liver, skin, bone and tendon. They found that the slowest turnover was in the collagen of the rat tail. This led them into the general field of collagen metabolism and they found by the use of isotopes that there are soluble precursors of collagen, which are later converted into the insoluble fibres (11, 13, 15, 19).

Having obtained a mass spectrometer at the NIMR, they were able to use the stable isotope $^{15}\text{N}$. This was administered in labelled yeast protein and demonstrated the high rate of breakdown into ammonia and yeast. However, the most important use of the radioactive and stable amino acids was in studies of porphyrin biosynthesis.

**Porphyrin biosynthesis**

During 1946 and 1947, because of the recent availability of isotopes (both radioactive and stable), Neuberger started to study porphyrin biosynthesis, an area in which his group made many significant contributions. Porphyrins are of considerable importance in a variety of areas of biochemistry and medicine because they are the precursors of haem (conjugated with proteins to form haemoglobins, myoglobins, cytochromes and catalases), chlorophylls and cobalamin (vitamin B$_{12}$). He had been impressed by papers of Shemin & Rittenberg (1946a,b) in which they indicated that the nitrogen atoms of glycine were the precursors of at least some of the nitrogen atoms of protoporphyrin. (The work of Neuberger's group for several years ran in parallel with Shemin's group in New York.) In collaboration with Helen Muir (F.R.S. 1977), they synthesized $^{15}\text{N}$glycine and $^{15}\text{N}$ethanolamine and showed that all four nitrogen atoms of protoporphyrin are derived specifically from glycine and not from ethanolamine (12). They also showed that the carboxyl carbon of glycine was lost in the conversion of this amino acid to protoporphyrin but that each pyrrole ring of the porphyrin contained one carbon atom derived from the $\alpha$-carbon of glycine. The latter also provided the four methylene bridges linking the four pyrrole rings (16).

Another problem that was addressed was of the intermediates and other precursors of protoporphyrin. $\delta$-Aminolaevulinic acid labelled with $^{14}\text{C}$ was synthesized by Scott (21, 22). This was used to investigate the complex pathway from porphobilinogen to protoporphyrin. Eventually the whole pathway from the condensation of glycine and succinyl-CoA, via $\delta$-aminolaevulinic acid to protoporphyrin, was unambiguously demonstrated in a series of papers by the groups of Neuberger (23, 24) and of Shemin (Shemin & Russell 1953). They had also discovered the origin of all the carbon and nitrogen atoms of protoporphyrin.

His group extended studies of porphyrin metabolism in the following 20 years. They investigated congenital and also acute intermittent porphyria, the disorder that caused the apparent 'madness' of King George III. By the administration of $^{15}\text{N}$ glycine to normal and porphyric individuals they were able to demonstrate the differences in the metabolism of the porphyrins that later led to other workers' finding that the disorder was due to a defective porphobilinogen deaminase.

Neuberger's group continued their studies of porphyrin formation in the purple photosynthetic bacterium *Rhodopseudomonas spheroides*. This organism was obviously much easier to use for metabolic studies than plants or animals, because cultures grow rapidly and can grow anaerobically in light or aerobically in both light and dark. It also had the advantage that it produced all three classes of tetrapyrrole, namely bacteriochlorophyll, haem
and vitamin B₁₂. With this bacterium it was possible to study the enzymes involved in the biosynthesis of haem and bacteriochlorophyll and to demonstrate which enzymes were activated or deactivated by light, oxygen and the state of the electron transport chain (29–31, 37, 38).

**GENERAL ACTIVITIES CONCERNED WITH BIOMEDICAL SCIENCE**

In 1990, Neuberger (55) gave his reasons for being involved in other activities:

> I have always felt that an academic scientist is in a privileged position in that he is paid for doing exactly what he wants to do, and this I believe imposes a duty and a responsibility to give some of his time to work which might be beneficial to society as a whole or to other scientists and academic colleagues. I felt this particularly when I was engaged in full-time research with little or no teaching.

His influence on British science extended well beyond his own considerable research contributions, because he was involved in many areas of the management of science. He was, at one time or another, a member of the Medical Research Council (MRC), the Agricultural Research Council (ARC), the Council of Scientific Policy, the joint MRC/ARC Committee on Food and Nutrition (of which he was Chairman) and the Independent Committee on Smoking and Health, and he was Royal Society Scientific Governor of the British Nutrition Foundation and later Honorary President of the Foundation.

He was also deeply involved with the Lister Institute of Preventive Medicine. From 1968 he was a member of the governing body and from 1971 its Chairman. The institute, which had a distinguished record in the biomedical field, was loosely connected to the University of London but relied for most of its income on vaccine production at Elstree. In the mid-1970s it became apparent that the financial situation was deteriorating. With considerable skill and tact, Neuberger and the committee managed to relocate staff, dispose of the buildings in Elstree and Chelsea and produce a considerable capital sum. This was used to set up a trust fund to endow fellowships in the biomedical field. These Lister Fellowships have attracted applicants of high quality and are yet another example of his foresight.

**ACTIVITIES IN INDIA AND ISRAEL**

In 1945 he spent four months as a consultant in nutrition to the medical directorate of the British Army in India, which he said was one of the most interesting experiences of his life. He became very interested in Indian civilization and culture and realized that the nutritional problems could not be understood without reference to the whole cultural and social situation. He revisited India for two lengthy visits in 1968 and in 1977–78 to advise the Indian MRC and the Nutrition Foundation of India on a variety of research activities.

After a visit in 1950 to the Weizmann Institute in Rehovot he became greatly involved in the academic life of Israel. At the Weizmann there were collaborations because of a shared interest in the biochemistry of carbohydrates. He also became a governor of the Hebrew University of Jerusalem and served as Chairman of the Academic Committee of the Board of Governors; he valued his contact with the other faculties of the Hebrew University. He enjoyed visiting Israel particularly because he had retained a knowledge of Hebrew from childhood. He and his wife had a flat in Jerusalem and were there frequently.
In 1947 he joined the board of the *Biochemical Journal* and in 1952 became Chairman. This involved a very heavy workload because he had to read the proofs of almost every paper that appeared in the journal. He also served on the committee of the Biochemical Society and was for two years chairman of the committee. He was elected an Honorary Member of the Biochemical Society in 1973.

In 1968 he joined the editorial board of *Biochimica et Biophysica Acta* and for much of that time was Associate Managing Editor. He was also heavily involved in a series of monographs entitled *Frontiers of Biology* (North-Holland Research Monographs) and in the general editing and planning of the *Comprehensive Biochemistry* series.

**Envoi**

Albert Neuberger was an outstanding scientist with an impressive intellect and a range of interests outside science. He was very well liked and respected by his colleagues for his tolerance, good humour and high scientific standards. He was also a devoted family man and leaves a widow, Lilian, and four sons, one of whom, Michael, is a distinguished molecular biologist and like his father is a Fellow of The Royal Society.

**Acknowledgements**

We are very grateful to Mrs Lilian Neuberger, Dr Michael Neuberger and Dr George Tait for their help and for their corrections to this text. We have also made extensive use of a Biochemical Society Archive video of Albert Neuberger in conversation with Robin Marshall and George Tait.

The frontispiece photograph was taken in 1961 by Godfrey Argent and is reproduced with permission.

**References to other authors**


The following publications are those referred to directly in the text. A full bibliography appears on the accompanying microfiche, numbered as in the second column. A photocopy is available from the Royal Society Library at cost.


Albert Neuberger


Biographical Memoirs


