ZAMBEZIA

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Edited by
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Zambezia is the journal of the University of Rhodesia and its publication has been made possible by the generous support of the Publications Committee of the University. The main focus of the journal, as its name implies, is South Central Africa; but inaugural lectures and articles of a more general interest will also be published. A series of monograph supplements to *Zambezia* is also provided to cover the main disciplines in the University (Education, Engineering, Humanities, Medicine, Science and Social Studies); and this series will not necessarily have the same regional focus as *Zambezia* itself. Two such supplements have appeared so far: *La Cloche Fêlée* by R. A. Lewis and *A Feedlot Profit Model* by E. M. Wilson; at least two are projected for 1977, on the development of maternity services in Rhodesia, and on the leisure activities of Europeans in Rhodesia.

Henceforth it is planned that *Zambezia* will consist of an annual volume issued in two parts.

ORDERS

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BIOCHEMISTRY AND BENEFIT TO MAN*

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A BIOCHEMIST HAS been defined as someone who 'talks of Chemistry to Biologists, of Biology to Chemists, and of women to other Biochemists'. However, nowadays there are many of the fair sex among the members of our profession and tonight I shall discard that ever-fascinating subject to talk to you of the development of the relatively young science of Biochemistry and to attempt to outline a few of the many ways in which it has been of benefit to man.

In order to do this, I intend to sketch for you the early historical development of the subject and then to describe how a knowledge of Biochemistry has benefited mankind in three fields, namely, in achieving an understanding of inborn errors of metabolism, in research on Cassava, and finally in the development of the ideas and concepts of rational chemotherapy.

Historical Outline. Biochemistry may be considered as the science which deals with the application of the laws of chemistry and physics to living organisms and, up to the present time, great success has been achieved in understanding how living organisms originate, grow, develop, and reproduce, through the operation of these laws which were originally formulated and applied only to explain the behaviour of inanimate matter. Furthermore, although there is much that we do not understand about living organisms, it has not been necessary to date to invoke a concept of a 'vital force' or to formulate new laws which fall outside of the domain of physics and chemistry. Consequently, the discipline of biochemistry developed out of chemistry on the one hand, and biology on the other, with substantial contributions from physiology, medicine, and agriculture. Originally, the term 'physiological chemistry' was used and it was not until well into the present century that what we now know as 'biochemistry' acquired its name.

There is much room for argument and discussion as to which were the principal events that led to the eventual development of the science of Biochemistry, so I would emphasize that the choice presented here is a purely personal one.

The story begins in 1752 when Réné de Réaumur embarked on some experiments to study the nature of digestion. His approach was one of which a modern-day biochemist would not feel ashamed. Taking advantage of the fact that birds of prey eject from their stomachs article of food that they

* An inaugural lecture delivered before the University of Rhodesia on 24 June 1976.

cannot digest, Réaumur fed a kite food encased in a small metal cage and examined it after it had been regurgitated. He found that the food had been partly eaten away by the solvent power of the contents of the stomach. Ten years later Lazarro Spallanzani, an Italian nobleman, confirmed Réaumur's observations with birds and extended them to other animals and to man. In fact, he made himself quite sick by feeding himself food contained in perforated wooden cubes which were later recovered for inspection.

Over the years 1742 to 1786, the Swedish pharmacist Karl Wilhelm Scheele isolated many compounds from natural sources, several of which he purified and obtained as pure crystalline organic chemicals. Thus, he prepared the protein casein from milk, glycerol from animal fats, uric acid from urine, and lactic acid from sour milk. He obtained citric acid from lime-juice, malic acid from apples and tartaric acid from wine. These substances however had to remain objects of curiosity until the fuller development of organic and analytical chemistry had taken place.

In 1780 Lavoisier first clearly stated the nature of respiration which he likened to a slow controlled combustion. Thus he stated 'respiration is therefore a combustion, slow it is true, but otherwise perfectly similar to that of charcoal'. Then in 1806 the great Swedish chemist J. J. Berzelius defined the term 'Organic Chemistry' in his book *Lectures in Animal Chemistry* as 'the chemistry of organized matter.' Implicit in this definition was the thought that the chemical substances produced by living things were fundamentally different from the 'inorganic materials' found in inanimate matter and that they constituted a separate field of study. This view persisted for a while but began to disappear following the synthesis by Friedrich Wöhler in 1828 of the 'organic' compound urea from the supposedly 'inorganic' compound ammonium cyanate. The synthesis was a simple chemical rearrangement brought about by heat as described by the equation below:

$$NH_4CNO = NH_2CO.NH_2$$

However the conversion of the inorganic compound into an organic one was not so clear-cut as might be desired, since the ammonium cyanate although considered an 'inorganic compound' itself was obtained via the heating of dried blood, horn and hides with iron and potash, definitely 'organic' sources. The final blow to the 'Vitalism' theory — the idea that the constituents of living organisms could only be made through the operation of some mysterious vital force — was dealt by H. Kolbe in 1845. Kolbe succeeded in synthesizing the organic compound acetic acid using only the elements carbon, sulphur, hydrogen, oxygen and chlorine.

His synthesis involved, first, the heating together of carbon and sulphur to form carbon disulphide (Equation 1). The carbon disulphide was then chlorinated to produce carbon tetrachloride (Equation 2). When the latter was passed through a red-hot tube, tetrachlorethylene and free chlorine were formed (Equation 3). In the presence of water and direct sunlight these two products combined to form trichloracetic acid (Equation 4). Reductive hydrolysis of the latter with potassium amalgam as a source of nascent hydrogen yielded acetic acid (Equation 5).

$$C + S \longrightarrow CS_2 \qquad \text{Equation 1.}$$

$$CS_2 + 2Cl_2 \longrightarrow CCl_4 + 2S \qquad \text{Equation 2.}$$

$$2CCl_4 \longrightarrow CCl_2 = CCl_2 + 2Cl_2 \qquad \text{Equation 3.}$$

$$CCl_2 = CCl_2 + Cl_2 + 2H_2O \longrightarrow CCl_3COOH + 3HCl \qquad \text{Equation 4.}$$

$$CCl_3COOH + 6[H] \longrightarrow CH_3COOH + 3HCl \qquad \text{Equation 5.}$$

In 1833, Payen, who was director of a sugar factory in Paris, and Persos, a university teacher, described the precipitation by alcohol of an extract of malt to give an impure preparation of diastase, the enzyme that converts starch to sugar. This was the first preparation of an enzyme and used a technique which is still widely used by biochemists to this day, that is the precipitation of enzymes by alcohols and other organic solvents. The recognition by Berzelius of the nature of enzymes led him in 1836 to develop the idea, and introduce the term, 'catalysis'. He wrote:

> we have good reason to suppose that in living plants and animals thousands of catalytic processes are taking place between the tissues and the fluids, producing the multitude of dissimilar chemical compounds for whose formation from the common raw material, sap, or blood, we had not been able to think of any cause, but which, in future we shall probably find in the catalytic power of the organic tissue of which the organs of the living body consist.

This was a remarkably clear enunciation and description of what we recognize nowadays as the field of 'intermediary metabolism'. It is interesting to note that it was not, as some might think, that the phenomenon of catalysis was discovered and enzymes were subsequently recognized to be catalysts, but that the whole idea of catalysis stemmed directly from an undertanding of the nature of enzyme action.

Fermentation. In the nineteenth century fermentation was a mysterious process by which sugar was turned into alcohol that had been known since Roman times. In 1818, Erxleben, a German industrial chemist, published a small book on fermentation in which he suggested that yeast was a plant whose growth caused fermentation. This entirely correct idea, however, appeared before its time and Erxleben's theory was overlooked. Then, during the three years 1835 to 1837 three separate individuals, Cagniard de La Tour, Theodor Schwann, and Kützing independently put forward the idea that yeast was a living organism and Schwann explained how this plant-like material was responsible for fermentation, converting sugar into carbon dioxide and alcohol — the idea put forward by Erxleben some 20 years earlier.

The scientific establishment of that time were reluctant to accept the truth of these ideas and in 1839, Wöhler, aided and abetted by Justus von Liebig, who was at that time the editor of *Annalen der Chemie*, published an anonymous article in that journal attacking Schwann's theories and ridiculing with heavy teutonic sarcasm the microscopic observations on which they were based. He described the observations that he himself had been able to make with the aid of a fictitious super-microscope:

> It is possible to distinguish clearly a stomach and intestine, the anus as a pink spot, and the urine-forming organs. From the moment

> they escape from the egg, these animals visibly gulp down sugar out of the solution and one can see it quite clearly arriving at the stomach. There it is instantaneously digested, as shown by the expulsion of excrement which follows promptly. In short, these infusoria feed on sugar and release alcohol from the bowels and carbonic acid from the urinary organs.

And all this in a yeast cell, not much more than a blob under many modern microscopes!

Baron von Liebig, who had done a great deal to apply the concepts and methods of chemistry to such diverse fields as agriculture, physiology, and pathology, was reluctant to admit that the chemical changes of fermentation required the mysterious 'vital force' of living organisms and believed that fermentation was the result of the shaking apart of the sugar molecule by the ferment (enzyme) arising from putrefying bodies. Thus, there ensued a lengthy debate between the main protagonists, Liebig and Pasteur, over the nature of fermentation. Pasteur upheld the view that there was 'no fermentation without life', and Liebig that fermentation was a purely chemical process catalysed by yeast or by some chemical substance derived from it.

Then, in 1897, Eduard Büchner and his brother Hans, working in Tübingen, suceeded by accident in obtaining fermentation without the presence of cells. The story of how they came to do so is a prime example of the well-known principle in science of 'Serendipity'. They were attempting to prepare an extract of yeast for the purpose of feeding it to patients to determine its therapeutic effects. The yeast was first ground with sand, then kieselguhr was added and the liquid was squeezed out in a press. Having obtained a yeast 'press-juice' in this manner, the next problem was how to prevent the liquid from going bad. Most ordinary antiseptics available at that time such as phenol and mercury were too poisonous for human consumption, so they hit on the idea of using the kitchen technique of preserving the juice by adding large amounts of sugar. Imagine their surprise when very soon the liquid began to bubble and froth and show all the signs of a vigorous fermentation!

Thus both Pasteur and Liebig were correct! There could be no fermentation without either chemical substances (enzymes) produced from living, or once-living cells, or, the presence of the cells themselves.

The fermentation of sugar by yeast-juice, although spectacular, comes to an end after a while, even though there is plenty of sugar remaining, whereas with living yeast the fermentation continues until either the sugar is all used up, or the alcohol level rises to a point where the cells can no longer operate. The British biochemists Harden and Young, in London in 1905, found that if inorganic phosphate is added at this stage of arrest the fermentation starts again and continues. They discovered that phosphate is required because, during fermentation, the inorganic phosphate is converted into organic phosphates, the sugar phosphates, and phosphate originally present in the yeast juice is used up and the fermentation is unable to proceed. When intact yeast cells are present, their content of phosphate is recycled and fermentation continues.

Their discovery, together with the later investigations of such well-known early biochemists as Embden, Meyerhof, Warburg, and Parnas, led to the elucidation of the glycolysis pathway (Fig. 1), sometimes known as the Embden-Meyerhof-Parnas pathway. Many of the biochemical reactions of this pathway are common to both the process of fermentation and to the conversion of glycogen to lactic acid which occurs in contracting muscles. Thus a whole era of Muscle Biochemistry was opened up. In 1929, Harden was awarded a half-share in the Nobel Prize for Chemistry for his part in these discoveries.

In 1926, James Sumner in America had a remarkable achievement. He purified the enzyme urease from jack-bean meal and succeded in crystallizing it and showed that it was a protein. Thus Sumner became the first man to crystallize an enzyme and to show that enzymes, although enormously complex, resembled other crystalline organic compounds such as cane-sugar or naphthalene. His results, however, did not go uncontested and they were vigorously denounced by Willstätter, a respected German biochemist who had concentrated many enzymes but had been unable to detect any protein in their solutions. These anomalous results were due to the insensitivity of the methods then in use to demonstrate the presence of protein rather than to the absence of the same. Thus, even as late as 1929, three years after Sumner's achievement, the *Encyclopaedia Brittanica* stated that 'Enzymes were formerly thought to be proteins, but this is no longer believed.' However, during the next few years, Northrup, another American biochemist, purified and crystallized several more enzymes and showed them likewise to be proteins — a view which is one of the basic tenets of modern-day Biochemistry.

That this year is the fiftieth anniversary of Sumner's discovery has not been overlooked in biochemical circles and recently Theorell recounted the following story. Svedberg was in his office in Uppsala when there came a ring at the door. He opened the door, and there stood a man, unknown to him, who said 'My name is James B. Sumner, I have crystallized an enzyme', Svedberg immediately concluded the man to be mentally ill and saying, 'Yes, yes, one moment' in a placatory manner, he hastily shut the door, locking it from the inside

From the time of Sumner's discovery the science of biochemistry was firmly established as a separate discipline and in the years to follow came to full flower in England, France, Germany and America.

Having presented this short historical sketch, I should now like to go on to outline for you some ways in which biochemistry has been of benefit to Man.

Inborn Errors of Metabolism. At the beginning of this century A. E. Garrod, a physician at St Bartholomew's Hospital, London, was studying the rare disorder known as alcaptonuria. This condition is characterized by the passing of urine of a normal colour and appearance, but which, on standing in the air gradually darkens and finally turns black — an occurrence, you can imagine, which would cause some concern to the unfortunate subject. This phenomenon is due to the presence in the urine of large quantities of a substance

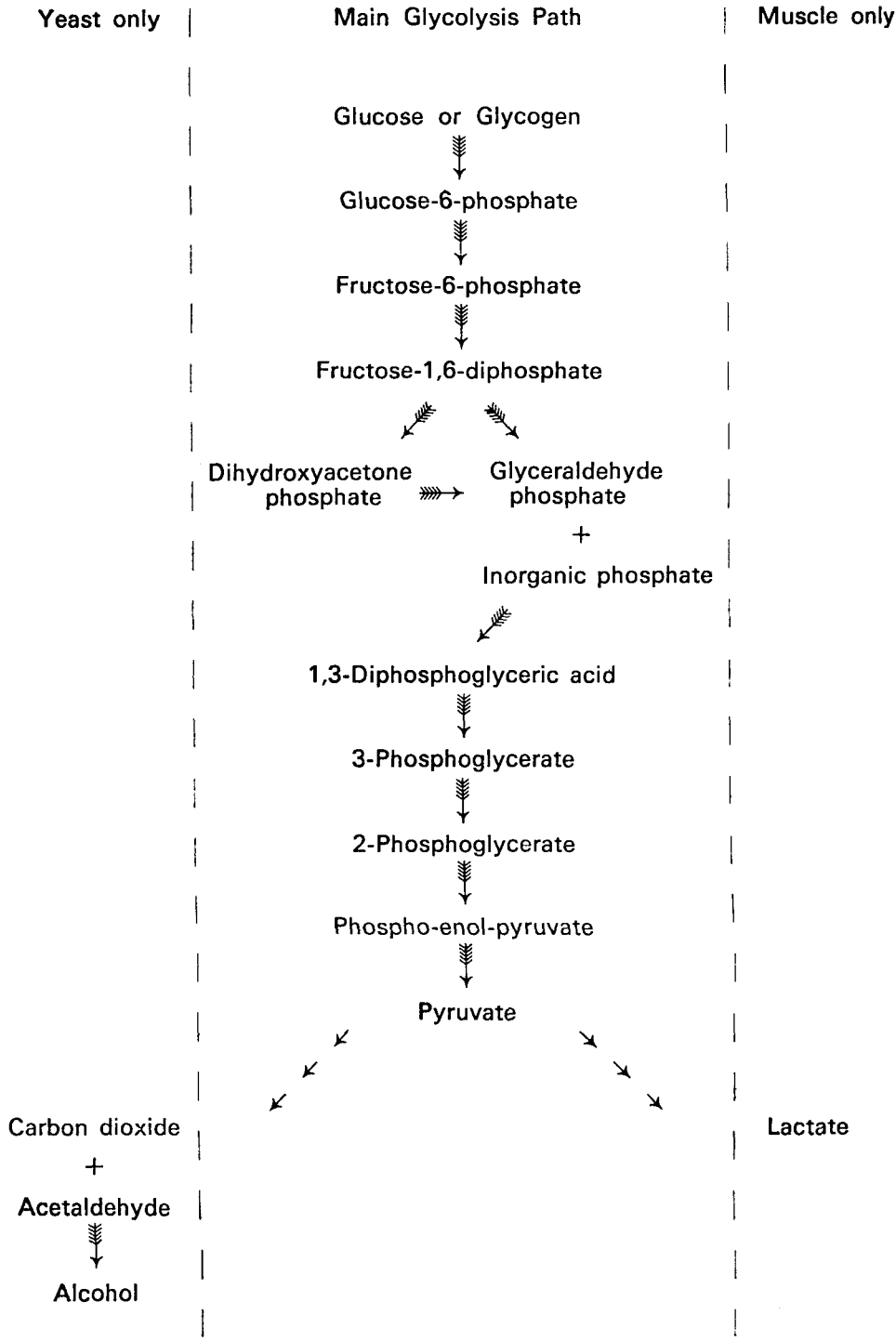

Figure 1: THE GLYCOLYSIS PATHWAY

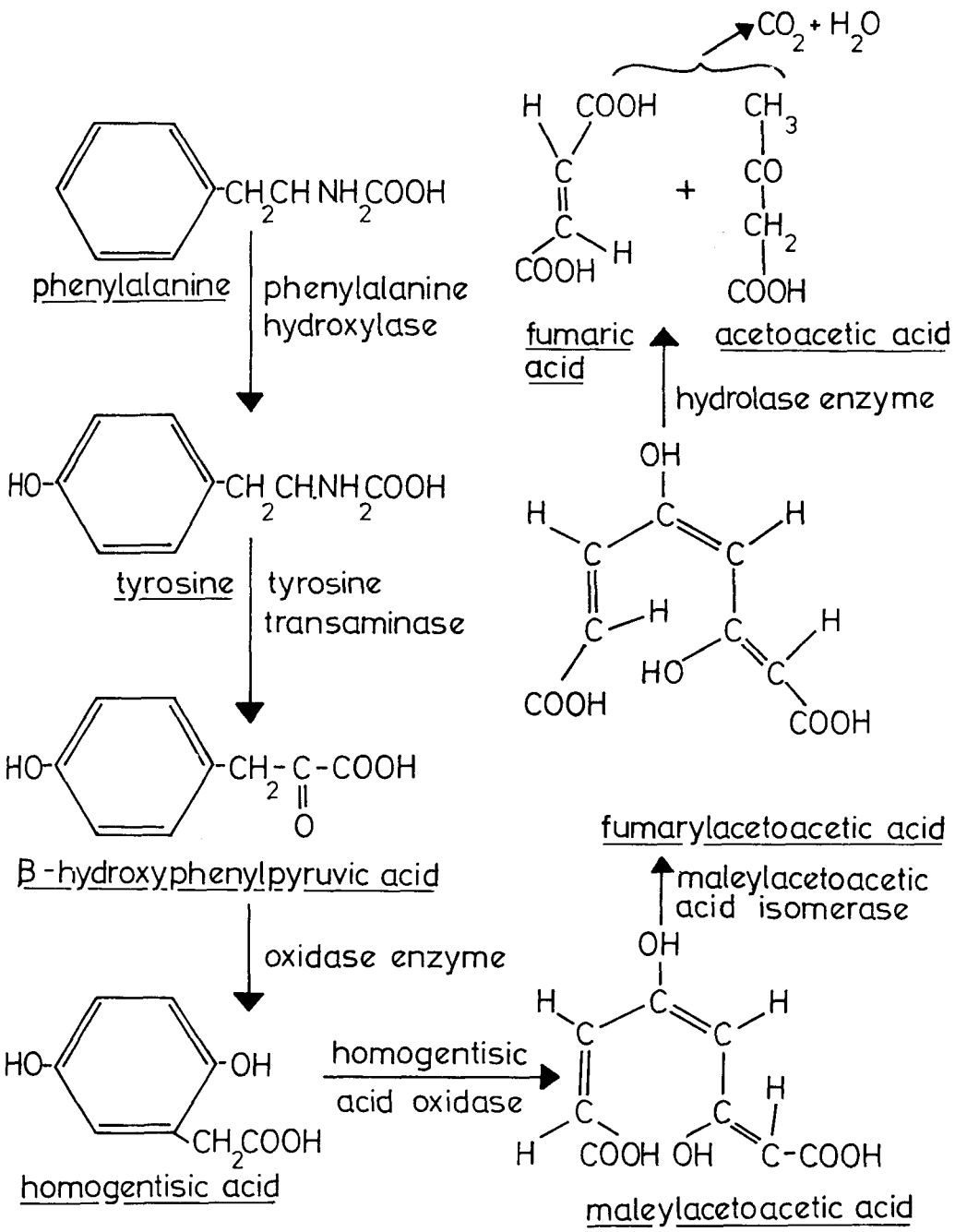

Figure 2: THE ENZYMATIC PATHWAY OF BREAKDOWN OF PHENYLALANINE AND TYROSINE

called homogentisic acid which is not present in normal urine and rapidly becomes oxidized in air to a black pigment.

Now, Garrod fed homogentisic acid to persons suffering from alcaptonuria and found that it passed through the body unchanged and was all excreted in the urine. When it was fed to normal people, however, the homogentisic acid was metabolized away and did not appear in the urine. Garrod also showed that the excretion of homogentisic acid was increased by feeding protein and that giving the aromatic amino acids phenylalanine and tyrosine alone would increase homogentisic acid output.

From these facts, he inferred that homogentisic acid was a normal intermediate in the pathway for the metabolic breakdown of these two amino acids and that, in a person inflicted with alcaptonuria, there was a lack of one or more of the enzymes responsible for breaking down these amino acids with the result that this compound accumulated in the tissues and subsequently overflowed into the urine. Correct as these ideas were, it was not until some 50 years later that the complete metabolic pathway for the catabolism of these two amino acids was fully worked out (Fig. 2) and the missing enzyme was identified as homogentisic acid oxidase, thus completely substantiating Garrod's hypothesis.

Garrod also investigated the distribution of this disorder among the various members of the family of each patient. At a time when the ideas of Gregor Mendel on inheritance were just beginning to be applied, he deduced that the condition could be explained as being due to the inheritance of a double dose of a rare Mendelian factor, or as we would say nowadays, a double dose of a recessive gene. Garrod introduced the term 'inborn error of metabolism' to describe this type of condition, indicating that an inherited fault in the body's metabolic machinery was responsible for the abnormal symptoms. This term is now widely used and the well-known geneticist Harry Harris in his latest book on *Human Biochemical Genetics* has listed some 25 different disorders associated with a hereditary deficiency of the corresponding 25 different enzymes and a selection of these is given in Table I.

Table I
INBORN ERRORS OF METABOLISM

Disorder	*Enzyme Lacking*
Hexokinase deficiency hemolytic anaemia	Hexokinase
Hereditary fructose intolerance	Liver aldolase
Favism	Glucose 6-phosphate dehydrogenase
Galactosemia	Galactose 1-phosphate uridyl transferase
McArdle's disease	Muscle phosphorylase
Congenital lactose intolerance	Lactase
Phenylketonuria	Phenylalanine 4-hydroxylase
Gaucher's disease	Glucocerebrosidase
Nieman-Pick disease	Sphyngomyelinase
Lesch-Nyhan syndrome	Hypoxanthine-guanine phosphoribosyl transferase

From our present-day understanding of these disorders of metabolism have arisen the possibilities of control and of remedial action. For example, some babies suffer from galactosemia, a disorder in which galactose accumulates in the tissues due to an inherited inability to metabolize lactose, and cataract and liver disorders result. These infants can now be kept free from symptoms by denying them milk of all types and feeding them a galactose-free diet. When they reach puberty another enzyme takes over the function of the one that is missing and thenceforth the children develop normally. In another defect of phenylalanine metabolism known as phenylketonuria, phenylpyruvic acid is excreted in the urine and the accumulation of this substance in the tissues soon causes mental deficiency. Although they cannot be fed a phenylalanine-free diet because phenylalanine is an essential body constituent, persons suffering from this defect can be helped considerably if they are maintained from birth on a diet low in phenylalanine, so that only the barest minimum for body requirements is provided.

Another way by which the incidence of 'inborn errors of metabolism' may be decreased is by 'genetic counselling'. Persons carrying defective genes who may not themselves suffer from any symptoms of disease may be identified by modern biochemical methods. Once identified the position can be explained to them and they may be given advice so that they do not unknowingly produce afflicted children. Finally, in the future, with the recent techniques of 'genetic engineering' there is the exciting possibility that one may be able to insert a gene into the organism, or into the egg cell, to replace the gene which has been identified as defective.

Cassava. The science of biochemistry has also brought great benefits to Man in connection with the growing and production, preservation and preparation of his food. As an example, I should like to describe some ways in which biochemical studies have been of service in a field with which I have had some personal connection.

The cassava plant is a very important root crop throughout Tropical Africa, South America and Asia. It is a plant bearing swollen edible tubers, which when cooked are not unlike potato and consist mainly of carbohydrate. Although low in protein, it is a good source of calcium, and the leaves (that can be cooked as a green vegetable) are rich in vitamin C. However, it has one serious nutritional drawback. The plant is poisonous! The

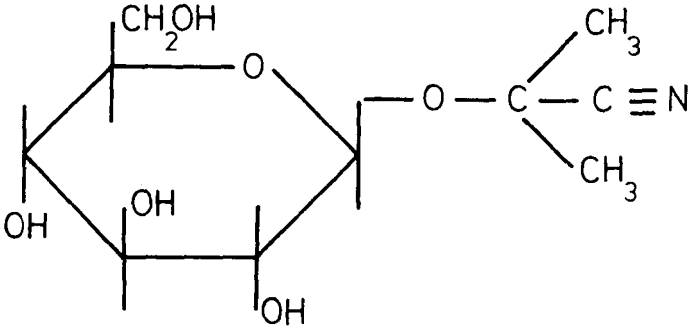

Figure 3: LINAMARIN

tuber contains a cyanogenic glucoside called linamarin (Fig. 3). This compound is the beta-glucoside of acetone cyanohydrin, akin to amygdalin a glycoside containing benzaldehyde and hydrogen cyanide which is the poisonous constituent of bitter almonds. It is a compound which can be broken down to produce cyanide. There is also present in the cassava plant, an enzyme called linamarase, which can hydrolyse linamarin to produce hydrogen cyanide, an extremely poisonous substance better known under the name of prussic acid. Hence the designation of the glucoside as 'cyanogenic' or cyanide-producing.

Traditional methods of preparing and cooking the cassava root result in the release and removal of much of the hydrogen cyanide. The tubers are first peeled and the extremely poisonous peel is thrown away. Then the peeled tuber is cut up and mashed or steeped in water so that a considerable part of the hydrogen cyanide resulting from enzymic action is removed in the wash-water or lost by volatilization to the air. Finally the tuber is boiled or roasted and more of the toxic material may be volatilized in these processes. Nevertheless, occasional incidents of acute poisoning due to the ingestion of cassava do occur, probably as the result of careless treatment of the tuber or of the cooking of an unusually toxic strain of the plant. Almost no research has been carried out on the question as to whether chronic poisoning occurs from the eating of cassava over a period of many years, although there are strong indications that such symptoms as blindness, liver enlargement, and disorders of the nervous system might be expected to result from such a staple diet. At the present time there is considerable interest by international aid organizations in methods of increasing the production of a less toxic grade of cassava which can be fed to both humans and pigs.

The release of hydrogen cyanide from cassava root was first demonstrated by Henry and Boutron Chalard in 1836. But it was not until 1906 that Dunstan and the same Henry (who must have been about 90 at the time!) isolated linamarin in a pure form and reported that hydrogen cyanide was liberated by hydrolysis of the glucoside with hot dilute acid. Much subsequent work

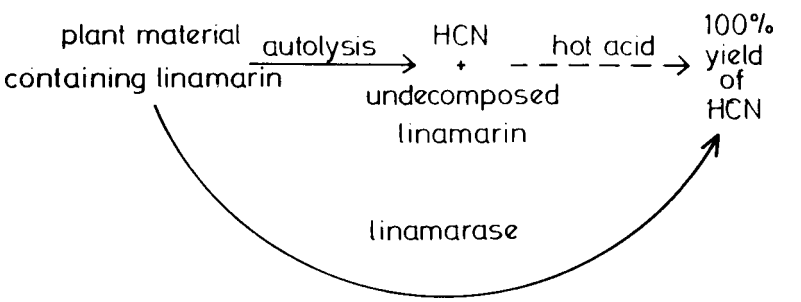

Figure 4: THE ASSAY OF LINAMARIN

has been carried out by agriculturists, medical men, and nutritionists, directed to studying the cultivation and improvement of cassava of low toxicity and the effects of eating it on man and animals. Nearly all of these studies have de-

pended upon an accurate measurement of the amount of cyanogenic glucoside present by means of the assay procedure outlined in Figure 4. The assay consists of a self-digestion, or autolysis, of the plant material, followed by a hot acid-hydrolysis and measurement of the hydrogen cyanide liberated. Although much useful information has been gathered from studies using this procedure, many of the results obtained have contained anomalies and inconsistencies.

More recent research, however, using improved procedures for purifying the glucoside and studying its biochemical properties has revealed that linamarin does not in fact yield significant amounts of hydrogen cyanide when treated with hot acid and that only treatment with linamarase can break down the glucoside to produce this substance. The former results merely reflected the ability of hot acid to facilitate the release of hydrogen cyanide already formed by traces of enzyme in the linamarin sample.

As a consequence of a misinterpretation of results in this obscure corner of natural product research, an unknown number of the thousands of measurements made in the past of hydrogen cyanide levels in the plant are incorrect. The amount of hydrogen cyanide actually measured depended more upon the amount of the enzyme linamarase in the sample and on the length of time allowed for the autolysis step, than on the amount of the glucoside present. Thus, only a fraction of the amount present may have been measured by the faulty assay procedure, which was based upon the false premise that hydrogen cyanide not liberated by self-digestion would be liberated in the second stage of the procedure by acid hydrolysis.

Later biochemical studies have led to improved procedures for the assay of the glucoside and it is hoped that future advances in our knowledge of cassava and of the toxic effects of the glucoside will henceforth rest on a sound analytical foundation.

The Development of Chemotherapy. In St Petersburg, in the year 1891, a Russian medical man, Romanovsky, was using a special microscopic stain (consisting of a mixture of eosin and methylene blue) that he had developed, to study the blood of patients being treated for malaria with quinine. Under the microscope he observed that the malarial parasites within the red blood cells of these patients showed signs of damage; the nuclei of the parasites were beginning to disintegrate and, when he observed blood from these same patients a few days later the parasites had completely disappeared.

Romanovsky concluded that quinine acted by damaging the parasite more than it damaged the host and he suggested that without doubt other compounds could be discovered that would cause maximal damage to the invading parasite and only minimal damage to the host. This idea, however, was not favourably received and was ignored, being ahead of its time, until some ten years later it was resurrected by Paul Ehrlich. Ehrlich coined the term 'chemotherapy', literally 'therapy by the use of chemicals', and he defined it as 'the use of drugs to injure an invading organism without injury to the host'. Ehrlich was fond of describing his ideas of chemotherapy in terms of a 'magic bullet' with which it was possible to shoot micro-organisms without

harming the human body. The idea was embodied in the 'chemotherapeutic index' which he defined as the ratio:

$$\frac{\text{Minimal Curative Dose}}{\text{Maximal Tolerated Dose}}$$

Thus, a drug which produces a cure when given at a dose of 1 mg/kg and causes harmful effects at a dose of 50 mg/kg has a chemotherapeutic index of 1/50 or 0,02. Nowadays we also speak of 'selective toxicity' and envisage a drug being specifically designed to inhibit some enzymic or metabolic process going on in an invading organism and at the same time being innocuous to the host.

Unfortunately, this goal of 'rational chemotherapy' is most often achieved through producing the 'chemotherapy' first by the blind, good old-fashioned method of 'trial and error' and the 'rationale' for the success or otherwise of the drug is only adduced at a much later date. For example, those most successful drugs, the penicillins, act by blocking the biosynthesis of muramic acid peptides in the cell walls of bacteria by virtue of their similarity in structure to part of the peptide molecule in the bacterium (Fig. 5). Penicillin kills growing bacteria because the newly synthesized cell wall is defective and cannot contain the high internal pressure which is a characteristic of the bacterial cell. As a result the cells burst and die. The human and mamalian

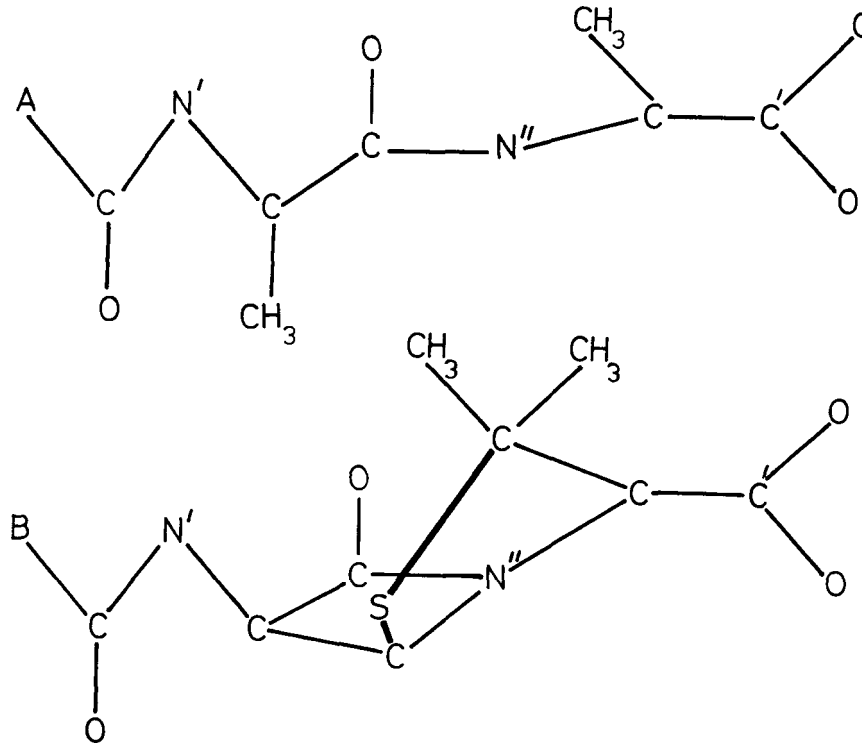

Figure 5: THE THREE-DIMENSIONAL STRUCTURE OF THE ACYL-D-ALANYL-D-ALANINE PEPTIDE OF THE BACTERIAL CELL WALL (A-CO- . . .) AND OF A PENICILLIN (B-CO- . . .) COMPARED

hosts do not have cell walls of this structure so a truly selective action on micro-organisms results. This mechanism of penicillin action was only elucidated, however, some 20 years after the introduction of the penicillin family into clinical medicine.

Nevertheless, as our knowledge of the principles of selective toxicity increases and our understanding of biochemical mechanisms in all sorts of living organism expands, so the ultimate goal draws nearer — the day on which a biochemist can sit down at his desk and, using his hard-gained knowledge of the differences in metabolism between a given parasite and its host, he may design a truly selective drug that will kill the parasite without harming the host in any way and thus fulfill Paul Ehrlich's dream of the 'magic bullet'[1]