# Contents

## Chapter 1

# Biochemistry and Geochemistry

> Carbon is unique among the elements in the number and variety of the compounds which it can form. Over a quarter of a million have already been isolated and described, but this gives a very imperfect idea of its powers, since it is the basis of all forms of living matter. Moreover, it is the only element which could occupy such a position. We know enough now to be sure that the idea of a world in which silicon should take the place of carbon as the basis of life is impossible; the silicon compounds have not the stability of those of carbon, and in particular, it is not possible to form stable compounds with long chains of silicon atoms.—N. V. Sidgwick, "The Chemical Elements and Their Compounds," Vol. I, p. 490.

In this book, we shall deal with the physical chemistry of biochemical systems derived from living organisms, or functioning within such organisms.

For the most part, we recognize what we mean when we speak of a living organism. Living things are always chemically complex; they contain certain very large organic molecules, such as the proteins and nucleic acids, the synthesis of which no chemist has yet achieved in the laboratory. They contain these substances, not in a random mixture, but in a highly organized system. They consume energy, not only in order to move or to grow, but in order to maintain themselves in a steady state—that is, they metabolize. By one fashion or another, they reproduce their kind. These characteristics—complex organized structure, metabolism, reproduction—may be taken as a convenient set of criteria for the general class of living organisms. Inevitably there are borderline systems, such as certain viruses, about which it becomes essentially meaningless to argue whether they are living organisms or not. Viruses are complex structures, and they reproduce, but their metabolism—at least over long stages of their existence—is virtually nil. In practice, however, the existence of these transition states between the living and the nonliving need not disturb us. We shall be concerned with living organisms, and the simpler systems derived from them, such as enzymes and their substrates, as systems which can be studied and analyzed by the methods of physical chemistry.

The principles involved are for the most part the same as those with which the physical chemist dealing with simpler systems is familiar, but the special properties of the complex structures produced in the living organism will lead us to emphasize some particular problems. The high degree of organization of biochemical systems means that a modification of one of the variables that determines the behavior of the system sets up interactions that produce changes in other variables. A simple and famous example is found in the study of solutions of the protein hemoglobin—the iron-containing, oxygen-transporting protein of the red blood cells. In most chemical systems containing liquids at equilibrium, one may equilibrate a liquid phase with a gas phase containing oxygen and carbon dioxide, and vary the partial pressure of either gas without appreciably affecting the amount of the other which the liquid can take up. If a solution of hemoglobin is in equilibrium with a gas phase containing both these gases, however, it is found that an increase in the partial pressure of carbon dioxide causes a marked release of oxygen from the solution to the vapor phase. Conversely, an increase of the partial pressure of oxygen causes carbon dioxide to be driven off. These interactions, which we shall consider later in detail, are of the greatest importance for the biological function of hemoglobin. To explain them, we must assume that oxygen and carbon dioxide both react, directly or indirectly, with the hemoglobin molecule, and that the effect produced by the one reaction is somehow transmitted through the molecule so as to affect the site at which the other reaction takes place. We might suppose that both oxygen and carbon dioxide react at the same site on the hemoglobin molecule, and that the interaction effects observed are simply the result of competition between the two molecules. This explanation indeed holds for the system hemoglobin–oxygen–carbon monoxide; but for oxygen and carbon dioxide the evidence is clear that at least two separate reactive sites are involved, and that the state of either one, as determined by the extent to which it has undergone its characteristic reaction, strongly influences the reactivity of the other.

This is a relatively simple example of organization in a biochemical system. More complex examples are found in the systems of enzymes which catalyze the successive steps involved in the biological oxidation of organic molecules; the whole process runs smoothly and is highly coordinated, to an extent that implies some degree of organized arrangement in the enzyme systems involved—an arrangement still very imperfectly understood. Examples of biochemical organization may be multiplied indefinitely, but these may suffice here.

Later we shall discuss highly complex biochemical molecules and systems. Before becoming involved in these complexities, however, it is well to consider some of the basic simplicities of the chemical elements, and their distribution in living organisms.

## Distribution of the Chemical Elements in Living Organisms

Living organisms as we know them utilize only a limited number of chemical elements. With very few exceptions the elements that have been clearly demonstrated to play a significant part in them are those with atomic numbers of 30 (zinc) or below. The major elements found in all living organisms are four, all with atomic numbers less than 9, namely, hydrogen, carbon, nitrogen, and oxygen. In the next row of the periodic table, sodium, magnesium, phosphorus, sulfur, and chlorine are elements of vital importance universally present. Passing beyond the electronic level of the completed argon shell with its 18 electrons, it is found that potassium, calcium, and iron are invariably essential constituents of living organisms though in relatively small amount. Cobalt, copper, and zinc, like iron, are almost invariably present although in relatively small traces. All these metallic elements, especially iron, play essential catalytic roles in certain enzyme systems, just as they function catalytically in many of the systems developed by the industrial chemist. Of the first thirty elements in the periodic table, from hydrogen to zinc, it is thus found that approximately half are invariably or frequently essential to the living organism. These first thirty elements are listed in Table IA, with a tabulation of their electronic structure and of their relative distribution in the universe at large, the earth's crust, and the human body. Comments on their biological significance are given in Table IB.

When we consider the other seventy elements of atomic numbers from 31 to 100, which are known today, it is remarkable that only three have been clearly recognized as important to the living organism. Two of these are halogens. Bromine (atomic number 35) is found only in traces in most organisms though in larger amounts in certain marine organisms. Iodine (atomic number 53), although present only in small amounts, is of fundamental and apparently universal importance. This one element of relatively high atomic number stands out in lonely eminence as a substance essential to life; all its neighbors in the periodic table appear to be either useless or harmful to living organisms, although rubidium has been found by D. Bertrand to be concentrated in certain fungi. In addition to these two halogens, molybdenum (atomic number 42) has very recently been reported as an essential constituent of certain oxidative enzymes, the molybdoflavoproteins. It is interesting that chromium (atomic number 24), which stands directly below molybdenum in subgroup VIA of the periodic table, has never yet been shown to play a role in any functioning biochemical system, in spite of the important technological use of chromium compounds in the tanning of leather.

In speaking of many of the elements as not essential to life, it must be remembered that we are speaking largely on the basis of ignorance. It is

## TABLE IA

### ATOMIC STRUCTURES AND DISTRIBUTION IN NATURE OF THE FIRST THIRTY CHEMICAL ELEMENTS

| | | Electronic structure | | | | | | | Relative abundance | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Symbol | Atomic number | 1 s | 2 s | 2 p | 3 s | 3 p | 3 d | 4 s | Universe (atoms per 10,000 atoms silicon) | Relative amount in earth's crust (atom %) | Human body (relative number of atoms) |
| H | 1 | 1 | | | | | | | $3.5 \times 10^8$ | | 9200 |
| He | 2 | 2 | | | | | | | $3.5 \times 10^7$ | | |
| Li | 3 | 2 | 1 | | | | | | 1 | | |
| Be | 4 | 2 | 2 | | | | | | 0.19 | | |
| B | 5 | 2 | 2 | 1 | | | | | 0.23 | | |
| C | 6 | 2 | 2 | 2 | | | | | 80,000 | | 1620 |
| N | 7 | 2 | 2 | 3 | | | | | 160,000 | | 370 |
| O | 8 | 2 | 2 | 4 | | | | | 220,000 | 62.55 | 3900 |
| F | 9 | 2 | 2 | 5 | | | | | 90 | | |
| Ne | 10 | 2 | 2 | 6 | | | | | * | | |
| Na | 11 | 2 | 2 | 6 | 1 | | | | 462 | 2.64 | 11.3 |
| Mg | 12 | 2 | 2 | 6 | 2 | | | | 8870 | 1.84 | 1.65 |
| Al | 13 | 2 | 2 | 6 | 2 | 1 | | | 882 | 6.47 | |
| Si | 14 | 2 | 2 | 6 | 2 | 2 | | | 10,000 | 21.22 | 0.14 |
| P | 15 | 2 | 2 | 6 | 2 | 3 | | | 130 | | 20.3 |
| S | 16 | 2 | 2 | 6 | 2 | 4 | | | 3500 | | 20 |
| Cl | 17 | 2 | 2 | 6 | 2 | 5 | | | 170 | | 5 |
| A | 18 | 2 | 2 | 6 | 2 | 6 | | | * | | |
| K | 19 | 2 | 2 | 6 | 2 | 6 | | 1 | 69.3 | 1.42 | 5.6 |
| Ca | 20 | 2 | 2 | 6 | 2 | 6 | | 2 | 670 | 1.94 | 34.4 |
| Sc | 21 | 2 | 2 | 6 | 2 | 6 | 1 | 2 | 0.18 | | |
| Ti | 22 | 2 | 2 | 6 | 2 | 6 | 2 | 2 | 26.0 | | |
| V | 23 | 2 | 2 | 6 | 2 | 6 | 3 | 2 | 2.5 | | |
| Cr | 24 | 2 | 2 | 6 | 2 | 6 | 5 | 1 | 95 | | |
| Mn | 25 | 2 | 2 | 6 | 2 | 6 | 5 | 2 | 77 | | 0.002 |
| Fe | 26 | 2 | 2 | 6 | 2 | 6 | 6 | 2 | 18,300 | 1.92 | 0.09 |
| Co | 27 | 2 | 2 | 6 | 2 | 6 | 7 | 2 | 99 | | |
| Ni | 28 | 2 | 2 | 6 | 2 | 6 | 8 | 2 | 1340 | | |
| Cu | 29 | 2 | 2 | 6 | 2 | 6 | 10 | 1 | 4.6 | | 0.0063 |
| Zn | 30 | 2 | 2 | 6 | 2 | 6 | 10 | 2 | 1.6 | | 0.038 |

Data for distribution of the elements in the universe and in the earth's crust from Mason (1952), pp. 21, 42.

* Estimates are relatively uncertain.

TABLE IB

BIOLOGICAL SIGNIFICANCE OF THE FIRST THIRTY CHEMICAL ELEMENTS

| Atomic number | Symbol | *Comments* |
|---|---|---|
| 1 | H | Universal and indispensable. |
| 2 | He | Inert. |
| 3 | Li | Apparently insignificant. |
| 4 | Be | Poisonous. |
| 5 | B | An essential constituent of plants; present also in traces in animals. Biological function little understood. |
| 6 | C | The essential basis of all forms of living matter. |
| 7 | N | Universal and indispensable. |
| 8 | O | Universal and indispensable. |
| 9 | F | An important minor constituent of vertebrate teeth; poisonous in excess. |
| 10 | Ne | Inert. |
| 11 | Na | Indispensable in animals; the predominant ionic constituent of blood plasma. Its significance in plants is more obscure than in animals. |
| 12 | Mg | Indispensable; an essential cofactor for many enzymes. |
| 13 | Al | Apparently of minor importance. |
| 14 | Si | Major element in the earth's crust; a structural component of diatoms and other forms. Probably of importance to many flowering plants. |
| 15 | P | Essential for biochemical processes. Energy transfer reactions in biochemistry generally involve phosphate esters. All nucleic acids and some proteins contain phosphorus. |
| 16 | S | Essential constituent of proteins, of coenzyme A, glutathione, and many other important biological compounds. |
| 17 | Cl | Almost universally present in animals; less important in plants. |
| 18 | A | Inert. |
| 19 | K | Major ionic constituent of many tissues; fundamentally important in such processes as nerve conduction. |
| 20 | Ca | Also of first importance; frequently significant as cofactor in enzyme reactions. Importance in plants less clear than in animals. |
| 21 | Sc | Apparently unimportant. |
| 22 | Ti | Apparently unimportant. |
| 23 | V | Essential constituent of hemovanadin, a metabolically active pigment in ascidians. Probably essential in lower plants. |
| 24 | Cr | Apparently unimportant. |
| 25 | Mn | An important catalytic factor in many biochemical reactions. |

TABLE IB (*Continued*)

| Atomic number | Symbol | Comments |
|---|---|---|
| 26 | Fe | Of pre-eminent importance as a catalytic factor in biological oxidations—in hemoproteins such as cytochrome oxidase, the cytochromes, catalases, and peroxidases—and for oxygen transport in hemoglobin. |
| 27 | Co | Essential constituent of vitamin $B_{12}$; required only in traces but important. |
| 28 | Ni | Apparently of minor importance in biology. |
| 29 | Cu | An essential constituent of important oxidative enzymes and of the oxygen transporting proteins of many marine animals (hemocyanins). |
| 30 | Zn | An essential constituent of the enzymes carbonic anhydrase, carboxypeptidase, alcohol dehydrogenase, and of some other important biochemical systems. |

only relatively recently, for instance, that the important role of molybdenum in living organisms has been appreciated; and biological functions for other elements, as yet unrecognized, may be discovered in future. In any case, many of the elements which we have classed as nonessential are often present in organisms, sometimes in considerable quantity. Thus although calcium is essential, and strontium and barium are not known to play any essential role, considerable amounts of the latter elements are often found in plants. For instance, Bowen and Dymond (1955) found large amounts of strontium, up to 2.6% of the total dry weight, in certain plants growing in English soils which were rich in strontium. Indeed a number of plants studied by them were found to absorb strontium preferentially, rather than calcium, from the surrounding soil. Appreciable amounts of barium were also taken up, in some cases as much as 0.7% of the dry weight of the plant, from soils rich in barium, although barium was never absorbed in preference to calcium. Such observations gain added interest from the fact that radioactive strontium ($Sr^{90}$) has become widely distributed over the earth, in small amounts, in the debris from the explosions of nuclear bombs. This radioisotope, with a half-life of approximately 27 years, is carried high into the stratosphere by the explosion of a thermonuclear bomb; it descends slowly into the lower atmosphere (the troposphere) over a period of many years and is carried down by rain onto the surface of the earth, where it is absorbed by plants, and thence passes into the bodies of animals which eat the plants (Libby, 1956). Like calcium it is concentrated preferentially in the bones and milk of these animals. In sufficient doses it produces bone tumors and other tumors in animals and presumably in man. The tendency to absorb strontium from the soil is most marked when the soil is poor in calcium, as for example in some regions in Wales. The extent of the hazard to human and animal life which this situation presents has been sharply debated; but, important as the subject is, we shall not attempt to pursue it further here.

The distribution of the chemical elements in plants and animals is profoundly different from that found in their surroundings. In order to grow and develop, they must concentrate some elements from their environment and reject others. Since these organisms emerged from the ocean and live on the surface of the earth or within its waters, it will be profitable to consider here the conditions of their emergence and the distribution of the chemical elements in the surrounding universe and in the crust of the earth and in the oceans in which life arose.

## The Relative Abundance of the Chemical Elements in the Universe

A large amount of information has now accumulated regarding the relative proportions in which the different chemical elements exist in the universe. Much of this is derived from spectroscopic studies of the sun and stars; chemical analyses of meteorites have also furnished important information. There are, of course, considerable variations in the composition of different types of stars, but for our purposes in this discussion these are relatively minor. Detailed tabulations will be found in several of the references given at the end of this chapter. The results are most conveniently summarized in the form of a diagram (Fig. 1). In this figure, the logarithm of the relative abundance of each element is plotted against its atomic number. The elements of odd and even atomic numbers are indicated by different types of symbols. Several notable features are immediately apparent from the diagram.

1. On the whole, the elements of low atomic number are much the most abundant, hydrogen and helium far more so than any of the others. Lithium, beryllium, and boron are much lower in abundance than any of their neighbors, but apart from this low region one may say in a general way that there is a gradual decline in relative abundance with increasing atomic number until values of about 40 are reached. Above atomic number 40, the relative amounts are distributed somewhat more evenly about a logarithmic value of $-2$ on the indicated scale.

2. Elements of even atomic number are almost invariably more abundant than the adjoining elements of odd atomic number. This relation was long ago pointed out, by Oddo in 1914 and by Harkins in 1917.

3. The value for iron (atomic number 26) is very much higher than that of any of the neighboring elements. Iron is at least a thousand times

as abundant as would be expected from an average curve drawn through most of its neighbors. Nickel (atomic number 28) is also well above the general level of such a curve, though not so high as iron.

4. Only eleven elements may be said to show really high abundance—H, He, C, N, O, Ne, Mg, Si, S, Fe, and Ni.

Undoubtedly these estimates will require some revision in future. Nevertheless, it is a striking fact that the relative proportions of the different elements are found not to differ very greatly throughout the entire known universe. This remarkable fact has naturally given rise to much discussion as to the origin of the elements in the early stages of the development of the universe. Attempts have been made to calculate the conditions which would give rise to the observed distributions, but this is not the place to enter into these cosmological discussions. Those who are interested can learn more about them by consulting such writings as those of Alpher and Herman which are listed in the bibliography.

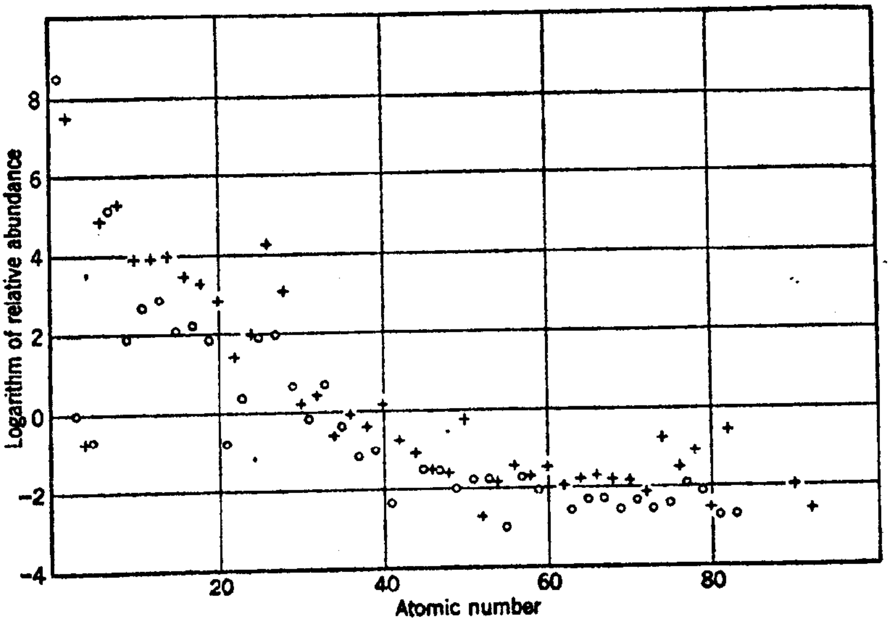

FIG. 1. Relative cosmic abundance of the elements as a function of atomic number. Elements of odd atomic number are denoted by circles, those of even atomic number by crosses. (From Mason (1952), p. 22.)

## The Structure of the Earth and Its Crust

The mean density of the earth is approximately 5.5, whereas that of the rocks on the earth's surface is only about 2.8. Therefore, at least a large part of the interior must have a density greater than 5.5 to account for that of the whole earth. Studies of earthquake waves, and other lines of evidence, have indicated that presumably there is a central core composed chiefly of iron, with some nickel, beginning approximately 2900 kilometers below the surface. The assumed composition of this core is closely similar to the observed composition of the iron-containing meteorites. Around this core is a mantle containing much less iron and large proportions of certain silicate rocks. Finally, near the surface is a relatively thin crust, also made up predominantly of silicates. The average composition of the crust is determined primarily by that of the igneous rocks, since the total amount of the sedimentary and metamorphic rocks is small compared to the bulk of the igneous rocks. In Table IA, an estimate is given of the average amounts of some of the most important elements in the earth's crust, based on studies by F. W. Clarke and H. S. Washington, and by V. M. Goldschmidt and others. It will be seen that the distribution of the elements in this crust is strikingly different in many respects from that of the universe as a whole. Hydrogen and helium are present in much smaller amounts, having been largely lost from the earth because of their volatility. Iron, although fairly abundant, is relatively much less so than in the universe as a whole; presumably most of the earth's iron has been concentrated in the core, leaving comparatively small amounts in the crust. The dominant elements are oxygen and silicon. Carbon, which more than any other element is characteristic of living organisms, is present in relatively minor amounts, being exceeded by at least a dozen other elements. Life has emerged and persisted in surroundings composed primarily of silicate rocks, with large amounts of water.

The structure of the earth's crust, as we know it, is the product of a long series of processes, involving the gradual selective crystallization of the most insoluble material from molten rock masses (magma) on cooling, and erosion and sedimentation processes due primarily to the action of water, continuing over vast periods of time. The details of these processes offer a fascinating study in physical chemistry. Many of the principles involved have now been worked out, owing particularly to the searching studies of V. M. Goldschmidt and his school—see, for instance, the books by Mason (1952) and by Rankama and Sahama (1950)— although most of the problem still remains to be explored. It would take us too far afield to attempt a discussion of the principles involved, but one interesting consequence of these natural processes is worth pointing out. It may be seen from Table IA that the cosmic abundance of magnesium is nearly twenty times that of sodium, and that of calcium is about ten times that of potassium. This accords with the general rule that elements of even atomic number are of higher cosmic abundance than their odd-numbered neighbors. Yet in the earth's crust all these four elements are of nearly equal abundance—a fact which can be explained in terms of the physical chemistry of the formation of the earth's crust, and which is certainly of major importance in determining the nature of the environment in which living organisms arose and evolved.

The mean elementary composition of living matter on the surface of the earth has been calculated approximately by the Russian geochemist Vinogradov. His data are largely derived from the wet wood of forest trees, for these make up about 80% of the living matter on land. These data have been supplemented, however, by a number of analyses of other kinds of organisms. The data for the major elements H, O, C, N, K, S, P, Ca, and Mg in living organisms are certainly satisfactory. Those for the minor elements are certainly much less reliable. A revised estimate of the total distribution of these elements in living organisms was presented by G. E. Hutchinson (1943), and the results are summarized in Fig. 2, which shows the comparison between the relative abundances of the first thirty-one elements in the cosmos and in terrestrial living matter. The general parallelism of the two curves is strikingly apparent. The upper curve in Fig. 2 for cosmic abundance of the elements, as given by Hutchinson in 1943, would require some revisions in the light of knowledge

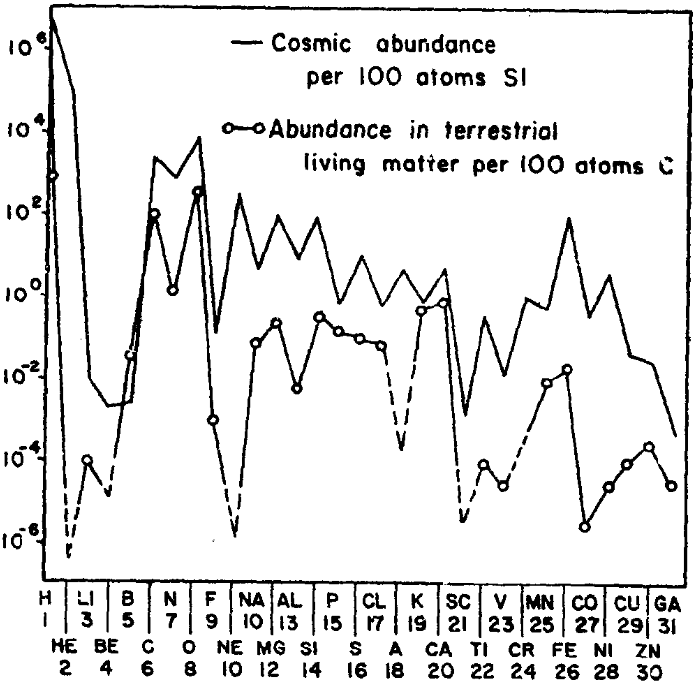

FIG. 2. Relative abundances of the first 31 elements in the cosmos and in living organisms on the earth's surface. (From G. E. Hutchinson, 1943.)

accumulated since. Such corrections, however, would not be great enough to alter the form of the curve in any very striking manner.

It may be noted that the abundance of carbon is high in both curves of Fig. 2, although a similar plot of the abundance of the elements in the earth's lithosphere would place carbon much lower on the scale. If we leave out of consideration the inert gases which, of course, cannot be retained by living organisms in significant amounts, the main biological elements are the cosmically common elements, especially H, O, C, and N. Silicon and aluminum, which are abundant on the surface of the earth. are much less prominent in the curves of Fig. 2.

## Early History of the Earth

It is generally believed that the sun, the earth, and the other planets were all formed from a common pool of primitive material. It had been widely held in earlier years that the earth was formed by condensation from a very hot system composed of incandescent gases. On the other hand, the prevailing view of many, perhaps most, recent workers is that it was formed by gradual accumulation of particles from a cloud of cosmic dust at relatively low temperatures. On either basis, it would be possible to explain the relatively small amounts of hydrogen and helium in the earth as compared with the sun or stars. If the earth was formed by condensation of a mass of hot incandescent material, the lighter gases would naturally tend to escape from the earth's gravitational field during cooling. On the other hand, if the earth grew from a gradual condensation of small solid particles at rather low temperatures, the very light gaseous elements would never have taken part in the accumulation at all. The fact that the heavy inert gases krypton and xenon are also of very low abundance in the earth as compared to their distribution in the universe at large would favor the hypothesis of a gradual accretion at low temperature. If they had condensed with other elements from a hot gaseous system, their mass is high enough so that gravitational attraction would have held them on the earth.

Even if the earth developed by slow accretion of particles from a cold cosmic dust cloud, it seems almost certain that it must have been very hot and molten at an early stage in its history. The assumption of such a molten state appears to be required by the marked stratification of density at different levels with a high concentration of iron and nickel in the inner core. The production of such heat, however, appears perfectly possible; the kinetic energy of the particles coming together to form the earth and the compression by gravitational attraction would generate great heat. Much heat was undoubtedly produced also by radioactive disintegrations which still continue. On the accretion hypothesis the primitive