TABLE 7

Depth in fathoms	Velocity		Percentage of correction			Maximum difference from adopted value	
	Maximum	Minimum	Maximum	Minimum	Adopted	Per cent.	Fathoms
600	819	809	2.4	1.1	2.0	0.9	5
1,200	816	811	2.0	1.4	1.7	0.3	4
1,800	817	814	2.1	1.7	2.0	0.3	5
2,400	821	818	2.6	2.3	2.5	0.2	5
3,000	825	823	3.1	2.9	3.0	0.1	3
3,600	830	828	3.7	3.5	3.6	0.1	4
4,200	835	833	4.4	4.1	4.2	0.2	8
4,800	839	838	4.9	4.8	4.9	0.1	5
5,400	844	841	5.5	5.1	5.4	0.3	16

As a test of this method, twenty-two soundings in the Pacific shown on page 22, Special Publication No. 108, were computed, using Table 5, and the results compared with those based on observed temperatures and salinities. The soundings ranged from 736 to 3,472 fathoms. The greatest difference was six fathoms and the average difference for the twenty-two, 2.5 fathoms without regard to sign. In six cases there was exact agreement.

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UNITED STATES COAST AND
GEODETIC SURVEY

THE IMPORTANCE OF MINUTE CHEMICAL CONSTITUENTS (INFINIMENT PETITS CHIMIQUES[1]) OF BIOLOGICAL PRODUCTS: NICKEL, COBALT AND INSULIN[2]

AT the end of the last century it was considered that plants and animals were composed of an association, under different forms more or less complicated, of about a dozen elements—carbon, hydrogen, oxygen, nitrogen, sulfur, phosphorus, chlorine, potassium, sodium, calcium, magnesium and iron.

Later, due to refinements of analytical chemistry, about an equal number of other elements were found in the organs of living species of plants and animals. Consequently, there may now be added to the above list silicon, boron, titanium, arsenic, iodine, bromine, fluorine, manganese, aluminium, zinc, copper, nickel and cobalt.

The proportion of the various elements which enter into the composition of an organism differs greatly according to whether they belong to the first list or to the second. Those of the former, aside from iron, are very much more abundant than those of the latter list, and make up more than 99.9 per cent. of the total weight of the substance, while iron and the elements of the second list make up the balance. That is to say, there are present only extremely small proportions of these latter elements.

The first eleven elements exercise an essentially plastic rôle in that they enter into the composition of the protoplasm, the nucleus and the cell walls, the reserve materials, the internal or external skeleton, the dissolved substances which maintain the rigidity of soft tissues, etc. Their utility is apparent at the first examination.

This is not the case with the other elements. On account of the very small quantities present, they can not, *a priori*, play the rôle of plastic elements, and the idea has been frequently expressed that they are of no physiological interest. Numerous and very careful experiments during the last dozen years have shown, on the contrary, that certain of these elements play a very important part as catalyzers of metabolism.

In 1912 I had the honor of presenting a paper at the Congress of Applied Chemistry held at New York,[3] in which this conception was developed, especially from the point of view of agriculture. I described my personal researches in which the intervention of manganese in the catalytic oxidation provoked by laccase was shown, and, furthermore, that manganese must be included among the elements necessary for vegetable growth. An application of these experiments has been the employment of manganese as a fertilizer.

Addressing myself to-day to a group particularly interested in questions of therapeutic chemistry, I wish to present the recent work which I have undertaken with some of my collaborators upon the importance of nickel and of cobalt in biology.

Following the discovery with M. Mokragnatz in 1922 of the presence of small quantities of nickel and of cobalt in all samples of arable soil which were examined,[4] we sought to ascertain whether these two

[1] The expression "infiniment petits chimiques" has a definite sense in French which can not be exactly translated into English. "Infiniment petits" was adopted by Pasteur and his associates to indicate microbes which were infinitely small living organisms responsible for profound changes. M. Bertrand by the modification "chimique" limits the application of the term to those chemical elements or complexes which, in extremely minute amounts, are responsible for a great variety of reactions occurring in biochemical systems.

[2] Address delivered by the director of the Biological Chemical Laboratory of the Pasteur Institute, of Paris, at the meeting of the American Chemical Society, on September 9, 1926.

[3] Transactions Eighth International Congress of Applied Chemistry, Vol. XXVIII, p. 30.

[4] Bull. Soc. Chim. de France, [4] *31*, 1330 (1922); *37*, 326 (1925).

metals were absorbed and retained by plants. The experiments demonstrated that this was the case.[5] Later, in collaboration with M. Macheboeuf, the study has been extended to the animal kingdom and it has been found that the bodies of man and of a great variety of animals contain very small quantities of cobalt and of nickel.[6] The amount present is of the order of a fraction of a milligram per kilogram of the fresh tissue.

Is the presence of these two metals in the organism purely passive, resulting from the gradual passing of nickel and cobalt from the soil to the plants and then to the animals by the agency of the ordinary laws of physical chemistry; or is it, on the contrary, due to the intervention of one or many biological processes? Upon first consideration it might be expected that a very long time would be necessary for solving this difficult problem. However, we have been fortunate in discovering a series of facts which, although they may not furnish a complete solution of the problem, already indicate the importance of nickel and cobalt from the biological and even the therapeutic point of view.

In determining the distribution of these two new elements of living material in various organs, we have been impressed by the relatively high content of these metals in the pancreas.[7]

We have therefore undertaken to demonstrate whether there is a relation between the two metals and the physiological action of this gland.

We have found in working along this line that insulin preparations contain considerable amounts of nickel and cobalt. On the basis of equal weights of sample, there are often hundreds of times more of these metals in insulin than contained in the tissues from which it was extracted.

Considering these results in comparison with the rôle played by manganese in the action of laccase, we have sought to learn whether nickel and cobalt intervene in some manner in the hypoglycemic action of insulin.

The experiments have shown that with certain preparations of insulin the simultaneous injection of a small quantity of nickel or of cobalt increases notably the quantity of sugar destroyed. We have made experiments upon rabbits[8] and dogs[9] and found in both cases an activation of the hypoglycemic power of the insulin.

[5] Bull. Soc. Chim. de France, [4] *37*, 554 (1925).

[6] Bull. Soc. Chim. de France, [4] *37*, 934 (1925); *39*, 942 (1926).

[7] Compt. rendus *182*, 1305 (1925).

[8] Comptes rendus *182*, 1504 (1926).

[9] Comptes rendus *183*, 5 (1926).

Should one on the basis of these experiments consider nickel and cobalt as the coferments of insulin in the same way that manganese is the coferment of laccase? Do they form a part of the molecule of insulin? Furthermore, are there two substances in insulin, or rather in the preparation of insulin, of which one depends upon the action of nickel and the other upon that of cobalt?

In order to reply to the first of these questions it is necessary to cause insulin to act *in vitro*, which has not as yet been done. It is possible that nickel and cobalt do not intervene in a direct manner in glycemia, but by the intermediary of a particular organ.

As for the other questions, they can probably be easily answered by means of experiments with pure insulin such as has recently been obtained in a crystalline state by Professor Abel.

Personally I shall not be surprised if a metal is not found as a constituent of the insulin molecule. It is possible that in the present case the phenomenon is analogous to that of the transformation of protrypsin into trypsin under the influence of calcium, and thus there is in the pancreas, and consequently in certain preparations prepared from it, one or two kinds of pro-insulin of which the transformation into insulin is conditioned by the presence of nickel or of cobalt.

An application may, however, be made of the facts which have been observed. It is the possibility of advantageously modifying certain preparations of insulin by the addition of suitable amounts of nickel or of cobalt.

But this is not the only application.

Since diabetes, or, more particularly, certain forms of diabetes, are the result of an anatomical or perhaps simply functional alteration of the pancreas, it is not illogical to examine whether it may not be possible to cure or at least alleviate certain cases of the disease by the introduction into the general circulation of small quantities of nickel or of cobalt.

M. Macheboeuf and I have begun such experiments, first with nickel or cobalt alone, and then with mixtures of the two. Encouraging results have been obtained. We have found,[10] and our observations have been confirmed by those of M. Rathery and of Mlle. Levina,[11] that cases of simple diabetes, excluding the consumptive type, may be benefited, sometimes even to the extent of the complete suppression of urinary sugar.

There is here a new and indeed unexpected application of the study, so full of promise, of the rôle of the "infiniment petits chimiques" in biology.

GABRIEL BERTRAND

[10] Comptes rendus *183*, 257 (1926).

[11] Comptes rendus *183*, 326 (1926).