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DEATH AND THE PLOUGHMAN

Drawing by Holbein (1497-1543)

Holbein's striking representation of the ever-watchful death figure has a significance, 400 years later, that will not escape the readers of this book.

SOIL, GRASS AND CANCER

*Health of animals and men
is linked to the mineral
balance of the soil*

André Voisin

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Organisation Society Ltd.*

1959

LONDON

CROSBY LOCKWOOD & SON LTD
26, OLD BROMPTON ROAD, S.W.7

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The text of this work, rewritten and enlarged, is based on the author's lectures and conferences at l'École Nationale Vétérinaire d'Alfort (Paris), and for Veterinary Societies in France and abroad, particularly at Bonn, Göttingen, (Germany), Dartington Hall and Barnstaple (England), Dublin and Cork (Eire).

Drawings from sketches by
MARTHE-ROSINE VOISIN

Made and printed in Great Britain by
Richard Clay and Company, Ltd., Bungay, Suffolk

FOREWORD

By ALLAN FRASER, M.D., D.Sc.

I CONFESS to finding this, the most recent book by André Voisin, intensely interesting. Its title might suggest superficially the speculative food faddist or the pseudo-medical crank at his very worst. In my opinion, Andre Voisin is neither a faddist nor a crank. His "rational" system of grazing, apparently the most highly productive method of grassland management ever designed, is sufficient proof of his practical capacity. Although in both his reading and his thought (and let it be understood that he is both extraordinarily widely read and an original thinker) Voisin covers a variety of apparently diverse subjects—soil science, biochemistry, plant physiology and medicine—it seems to me that his general approach to all biological problems is that of the intelligent and observant farmer. Now, my experience of both teaching and research in agriculture has given me an ever-increasing respect for the views of the intelligent and observant farmer. I use the words "intelligent and observant" with purposeful deliberation because, of course, admittedly, one meets with many farmers who are neither. Yet I am convinced that, on the whole, farmers are more intelligent and observant than the average agricultural scientist, the most probable reason being that while a farmer who makes momentous blunders soon becomes bankrupt, an agricultural scientist may secure at the best honour and promotion, at the worst superannuation, before his errors are found out!

It is possibly because Voisin is essentially a farmer with his outlook based on the traditional wisdom of the peasantry of his native France that, sometimes against my scientific judgement, I find myself so much in agreement with many of his ideas. On the very last page of the text, as though terminating a scientific dissertation with a Confession of Faith, Voisin writes: "This is the scientific philosophy that I have evolved for myself through watching my cows at grass."

My sympathy with many of Voisin's frankly speculative views may well be due to the fact that while I have kept watch over sheep in Scotland he has kept watch over cows in France. The intelligent observation of livestock in the field forms—I am certain of it—one of the soundest apprenticeships to biological science. It is one way, and there are not so very many other ways, of keeping sight of the wood through a mist of trees.

Without a doubt, the health of both animals and men is linked to the mineral balance of the soil. The realisation of that fact is neither new nor specific to Voisin. Much of the argument contained in this book was stated on rather different evidence but with equal force by McCarrison. The reputation of the Rowett Institute at Aberdeen was founded on Orr's

earlier researches on that very subject. I can recall evening sessions in the sparsely furnished sitting-room of an Argyllshire hill sheep farm away back in the early 1930s when a group of four men were discussing this very problem with equal earnestness and, without any disrespect to Andre Voisin, possibly with an even profounder knowledge. Those four men were Dr. John Orr (now Lord Boyd Orr), the founder and originator of the World Food and Agriculture Organisation; the late Professor J. J. R. Macleod, a co-discoverer of insulin; the late Professor T. J. Mackie, of the Chair of Bacteriology in Edinburgh University; and my humble self. As a relatively young man I had the privilege then of listening to the fascinating speculations of three very learned and distinguished scientists on the relationship of the minerals in the soil and of those in the blood; of the connection between the biochemistry of nutrition and that of immunology, of the future possibilities of that very "protective" medicine on which Voisin founds his hopes.

I do not recall hearing cancer specifically mentioned or discussed. It is a long time ago now, and I may well have forgotten. If, as Voisin suggests, the control and prevention of cancer lies in a better understanding of human nutrition it would indeed be a notable advance. The modern treatment of cancer is admittedly unsatisfactory, at its best palliative and symptomatic, at its worst a progressive mutilation. It would, therefore, be a very good thing were Voisin's hypothesis proved true. I should be guilty of hypocrisy, however, were I not to confess that I still find that hypothesis just a little too simple to be altogether true.

*University of Aberdeen
May 1959*

ALLAN FRASER

FOREWORD

By H. M. SINCLAIR, D.M., M.A., B.Sc., M.R.C.P., L.M.S.S.A.

THERE is little doubt that human nutrition is the most important problem confronting mankind at the present time. The problem is one of both quantity and quality. It is estimated that at present two-thirds of the world's population, of 2,800 million, are underfed and this population is increasing by geometrical progression at a rate that will double it within 50 years. There are also problems of quality, for the more privileged third of the world's population increasingly consumes processed and sophisticated foodstuffs.

In order to keep pace with the increasing population and to try to eliminate the hunger that already exists, more food must be produced and made available to the people who need it. This can be done by making one blade of grass grow where none grew before—by bringing new lands into cultivation; or it can be done by making two blades grow where one grew before—by increasing yield of foodstuffs through better agriculture, better seeds, fertilisers, pesticides. All these practices create problems. Intensive agriculture removes elements from the soil—which may be naturally deficient in required elements, as Swiss soil is in iodine—and chemical fertilisers often do not necessarily replace what is removed; further, as M. Voisin shows, they may create imbalances. Substances may accumulate on the soil or in the crops grown upon it, such as oestrogens fed to cattle or insecticides sprayed on plants. It is estimated that in the year 1951 the quantity of pesticides produced in the United States was sufficient to kill six times the population of the world. Antibiotics, injected into animals before slaughter or applied to the udder of the cow to treat mastitis, appear in human food; tranquillisers given to hens or cows or steers pass into eggs or milk or beef. Manufacturers of food make it attractive by adding flavours and colouring substances, and preserve it in various ways to increase its shelf-life and enable it to be shipped around the world. We have little idea of the effect on man of some of these various practices.

M. Voisin informs us that this book is a preface to a larger work on *The influence of the soil on the metabolism of the living cell*. This is a subject we know little about. Further information is urgently needed. The need is twofold: first, to collect and integrate existing knowledge; secondly, to supply by research the tremendous gaps that exist. It is absolutely essential for the world's economy that we use chemical fertilisers, and use them increasingly; pesticides and other agricultural advances are also essential. But, as Sir Robert McCarrison and others have stressed in the past, we must watch what we are doing. M. Voisin has put together much recent information in this book; not everyone will agree with his provocative

conclusions, but he states the evidence for them so that those interested in this important subject of the soil and human nutrition can read further and form their own conclusions.

H. M. SINCLAIR

Magdalen College
Oxford
June 1959

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To the Reader

IT is my hope that this book should be intelligible to the educated reading public with no special scientific or technical background. Equally, however, would I wish it to be read by those with a scientific training, not only as a matter of interest but also as a source of information. What is presented, therefore, is neither a grossly popular version nor a highly specialised work.

With these two groups of reader in mind certain chapters have been marked for the attention of, or omission by, either the specialist or non-specialist. The *non-specialist* reader may be content with omitting such text as is marked for the specialist and overlooking footnotes except where they provide useful explanations of scientific terms he may not understand. Likewise he may omit certain chapters, for, as is stated at the beginning of these, their reading is not essential to the understanding of the succeeding chapters. Tables and chemical formula, all of which are separate from the text, may also be omitted. The *scientific* reader, on the other hand, will be able to, and no doubt will, read the entire contents. His indulgence with certain footnotes explaining words familiar to all specialists is requested: these are intended for the general reader and are marked thus: (*).

Bracketed figures thus (338) signify numbered bibliographical references at the end of the book.

The scientific reader may frequently be disappointed at not finding fuller information on a subject in which he is particularly interested. Some of such demands for further information may be met by my next extensive work on "The influence of the soil on the metabolism of the living cell", to which this present volume is but a preface.

CHAPTER 1

"Remember that you are dust"

The "dust" of our cells is the dust of the soil

WE should frequently meditate on the words of Ash Wednesday: "Man, remember that you are dust and that you will return to dust." This is not merely a religious and philosophical doctrine but a great scientific truth which should be engraved above the entrance to every Faculty of Medicine throughout the world. We might then better remember that our cells are made up of mineral elements which are to be found at any given moment in the soil of Normandy, Yorkshire or Australia; and if these "dusts" have been wrongly assembled in plant, animal or human cells the result will be the imperfect functioning of the latter.

The living organism is the biochemical photograph of the environment

Our ancestors were well aware of the fact that it is this "dust" of the soil that finally determines vigour and health. At a time when metabolism, enzymatic functions, etc., were unknown, what they said was that *"the animal is a product of the soil"*.

Then, as now, certain areas were famous for stock-rearing, whether cattle or horses. It was a recognised fact that a Percheron horse removed from the French soil of Perche radically changed its character within a few generations. In the Ukraine I myself saw Percherons which had been imported at the beginning of the present century and pure-bred since. They still had much of the conformation and characteristics of the Percheron, but were hardly any bigger than the Cossack horses.

The belief of our grandparents that "the soil makes the animal" can be expressed today in more modern terms, which, however, are no more than a copy of the words of old. "The organism (animal or human) is the 'biochemical photograph' of the environment in which it lives, particularly of the soil which manufactured the nutrients for it."

Difficulties of studying the influence of the soil on Man

This "biochemical photograph", unfortunately, is going to be particularly difficult to obtain in the case of Man. For it is not a matter of a single photograph but of a whole photographic collection involving many pictures of very different environments.

Modern civilisation has multiplied means of transport, with the result that our diet today includes wheat from Canada, oil from Senegal, oranges from Spain, etc. Our cells therefore contain mineral elements originally existing in the soils of all these various countries. The time for people living in small rural communities and making do with the produce of their own fields and the water from their own springs for their sustenance is past. In these days it was easy enough to track down the deficient local "dust" giving rise to malfunctioning of the human cells and causing goitre, for example. It is much more difficult today to determine the influence of the soils of England, Senegal, Spain, etc., in causing disorders in the functioning of the cells of one man or group of men.

Grass provides a "biochemical photograph" of the soil

It will always be difficult, therefore, to see what relationship exists between the *soil* and cell metabolism in *Man*.

But we are lucky in that grass establishes a close connection between soil and *animal*, generally for eight months in the year. This relationship reveals the profound influence exercised by the soil on cell metabolism in the *animal*, which is very similar to cell metabolism in *Man*.

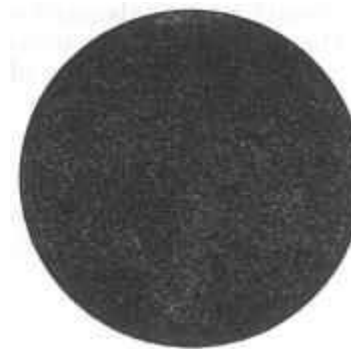
Thanks to grass and the grazing animal we will be able to get a splendid "biochemical photograph" of the soil. And grass will be the means—and an admirable one at that—used to show, from different and often unexpected points of view, how the elements of the soil control the functioning of our cells.

The search for general principles

The fifty examples or so given here have been chosen from among those cited in my lectures delivered at the National Veterinary College at Alfort (Paris). No attempt will be made to go into each of these examples in detail. The primary aim is to draw a general principle from each on the basis of which it should then be possible to anticipate, with reasonable probability, the laws of *protective* medicine, that great medical science of the future.

Philosophy of biological science

The words "with reasonable probability" are expressly used, for the *unknown* here will occupy infinitely more space than the *known* facts. Biological science is still young, and in speaking of the little that we know, we should keep our eye fixed on the innumerable facts of which we have no knowledge whatever.



WHAT ONE DOES
NOT KNOW

• WHAT ONE KNOWS

"The value of what one knows is doubled if one confesses to not knowing what one does not know. What one knows is then raised beyond the suspicion to which it is exposed when one claims to know what one does not know."

SCHOPENHAUER.

FIG. 1. My philosophy of biological science—compare with the works of the British pioneer of soil science, Sir John Russell, speaking in London in 1958: "While we have learnt a lot in the last fifty years the most important thing we have learnt is that the part of nature that we do not know is infinitely greater than the little bit of it that we think we do."

Fig. 1 illustrates the philosophy which, to my mind, is indispensable to progress in biological science: the small dot represents what is known, while the large black circle is the symbol of everything as yet unknown. If progress is to be made in the biological sciences the large circle must be the object of much more attention than the small dot.

Assembling "the dusts" of the soil

In 1897, for the first time, Gabriel Bertrand of the *Académie d'Agriculture*, succeeded in showing that a "dust" of the soil, that is to say a mineral element in trace form, was essential to the functioning of living cells. All observations have since confirmed this discovery.

An attempt will be made in this book to show how "dusts" of the soil are "assembled, bolted and screwed" to form the cells of our body and allow them to function. The special aim will be to demonstrate how illness can be due to an upset in the balance of this "assembly".

CHAPTER 2

*The mineral element of the soil modifies the
composition of the organic matter of
the plant*

The "Ash Mentality"

IN order to judge the effect of a mineral element on the quality of the plant, the variations of the content of this mineral element in the plant are determined by examining the residual ash of the plant after being burned. For example, phosphate is applied to the soil, and the extent to which the phosphate content of the grass is increased is measured. If the content of phosphate of the grass increases, it is accepted that it has a higher nutritive value for the animal, as it will consume a food richer in phosphate (with certain reservations concerning other factors).

This conception of the analysis of the mineral elements of the plant has been called by Albrecht (2, 26, 335) (Director of the Soil Department of the University of Missouri): "*Ash Mentality*".

It is probable that the American scientist in using the word "ash" has, with good reason, wished to suggest the idea of *death*, to which he opposes the "*Living* utilisation theory".

It is this "living" theory, which I shall try to explain, showing how the *mineral* matter of the soil modifies profoundly the *organic* matter and the metabolism of the cell, vegetable or animal.

Tryptophan

It is known, protein is constituted from amino-acids. One might say that the amino-acids are the bricks from which proteins are constructed. In order not to complicate the question and for the benefit of readers without a knowledge of biochemistry, I will deal with only three amino-acids, firstly, tryptophan and, subsequently, the two amino-acids containing sulphur, namely, methionine and cysteine. (See formulas in Figs. 2 and 3 on p. 6.)

Tryptophan is what is called an *essential* amino-acid, that is to say, an amino-acid which the animal or Man must find ready-made in the

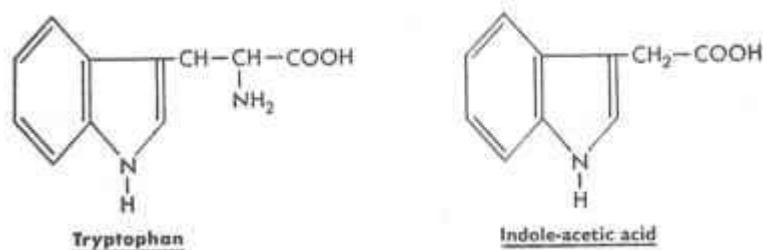


FIG. 2. Formulas of tryptophan and indole-acetic acid.

food because their cells are incapable of synthesising it, which the plant cell can do.

From the point of view of the plant, it is necessary to emphasise

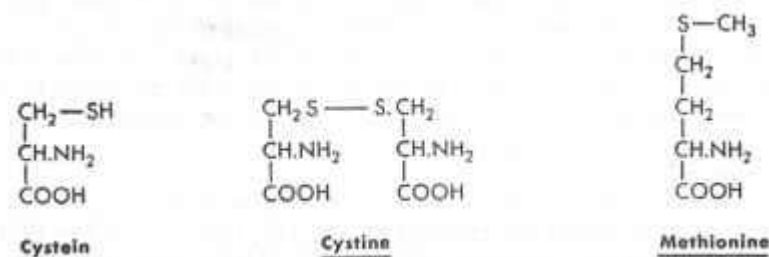


FIG. 3. Formulas of sulphur-containing amino-acids.

that the formula of tryptophan (indole-alanine) is very close to that of indole-acetic acid, which is the growth hormone of plants. (*)

We now proceed to show how the mineral elements of the soil modify the tryptophan content of the plant.

Influence of calcium and phosphorus on the content of tryptophan in agrostis

Table 1 on p. 7 shows that with a small application of phosphorus and calcium to the soil a gram of dry matter of agrostis contains 1.38

(*) This hormone can indeed be produced by the plant from tryptophan, thanks to certain enzyme mechanisms. This is, for example, proved in a simple experimental manner. When incubated under aerobic conditions, leaves impregnated with tryptophan make considerable quantities of indole-acetic acid in a short time.

mg. of tryptophan (335). But if we apply to the soil greater quantities of phosphorus and calcium the content of the dry matter in tryptophan increases to 2.65 mg.—almost double the amount.

TABLE 1

Influence of calcium and phosphorus on the tryptophan content of agrostis

Calcium content of the soil	Phosphorus content of the soil	
	High	Medium
	Milligrams of tryptophan per gram of dry matter	
High	2.65	2.38
Medium	2.21	1.88
Low	2.09	1.38

From Sheldon (335).

We, therefore, can better understand that the application of basal dressings of fertilisers allows more vigorous *growth* of the grass, since the application leads to a higher content of tryptophan and consequently a higher content of the *growth* hormone (indole-acetic acid), which manifests itself by an increase in yield.

The calcium and phosphorus have modified the organic matter of the grass

We have in this first example a confirmation of the fact that grass has its organic matter, that is its own cellular structure, modified by the application of calcium and phosphorus to the soil.

This is a much more important phenomenon than the modification of the calcium and phosphorus content of the grass as a result of the application of these elements to the soil.

Another example of this influence is given below.

Trace elements—factors in the manufacture of living matter

Trace elements are so named because they exercise their action on the mechanism of life even when they are present in very small amounts (parts per million or even less) in the soil or the living cell.

We know today the reason of this enormous influence. A trace

of these mineral elements is necessary to render active the enzymes, (*) which are the catalysts in the synthesis of living matter. One can almost say: *the trace element is the catalyst of the catalyst.*

Influence of boron on the content of tryptophan in lucerne

Table 2, below, shows the variation of the content in tryptophan of lucerne as a function of the content of boron in the nutritive solution in which this lucerne is grown (355).

When the concentration of boron in this solution passes from 0.22 to 1.08 parts per million the content in tryptophan of the lucerne increases from 1.36 to 2.55 mg./g. of dry matter, that is to say, it is almost *double*.

TABLE 2

Influence of boron on the tryptophan content of lucerne

Lucerne hay	
Boron in the nutrient solution (p.p.m.)	Tryptophan (mg./g.)
0	1.27
0.22	1.36
0.44	2.17
1.08	2.55

N.B. (1) The experiments were made with nutrient solutions, and the boron content shown represents the parts per million of that element in the solution.

(2) The tryptophan content is shown in milligrams per gram of dry matter.

From Sheldon (335).

Nitrogenous fertilisers in certain cases improve the composition of the "crude" protein of grass

Nitrogenous fertilisers used judiciously on a pasture, on condition that the appropriate "rest period" is observed,(**) can greatly increase the yield of grass. It seems that in addition, if the grass is not used when too young, the nitrogenous fertiliser can not only increase the nitrogen content of the grass, but also perhaps improve the biological value of the protein.

(*) Enzymes are also called ferments or biocatalysts. Their presence in living cells is enough to bring about certain chemical reactions or series of chemical reactions.

(**) See *Grass Productivity* (388).

Table 3, below, shows the influence exercised by the application of sulphate of ammonia and nitrate of soda on the composition of the nitrogenous matter of Italian rye-grass.

TABLE 3

Influence of nitrogen fertilisers on the composition of the protein of Italian rye-grass

	Without fertiliser	Sulphate of ammonia		Nitrate of soda	
Quantities of nitrogen applied per acre (lb) (bracketed figures show kg/hectare)	0	19 (22)	39 (44)	19 (22)	39 (44)
Percentage of N in dry matter	2.5	2.6	3.0	2.9	3.1
Percentage of total N in the form of α -amino N in the following amino-acids:					
Leucines	9.4	10.1	11.2	9.8	11.7
Phenylalanine	2.0	2.4	2.5	2.5	2.4
Tryptophan	0.8	1.1	1.2	1.3	1.3
Aspartic acid	5.7	4.9	4.3	4.9	4.0
Glutamic acid	7.2	6.1	5.9	6.0	5.0
Arginine	4.2	5.0	5.1	4.9	5.3
Lysine	2.9	3.3	3.4	3.6	3.4

From Smith and Agiza (340).

Without the application of nitrogen there is only 0.8 per cent of the total nitrogen in the form of nitrogen of tryptophan (an essential amino-acid). The proportion increases respectively to 1.2 and 1.3 per cent or, approximately, 50 per cent more, when one applies 39 lb./acre [44 kg./ha.] of nitrogen in the form of sulphate of ammonia or nitrate of soda.

It seems, then, that in this case the application of nitrogen fertiliser has resulted in an increase of the real nutritional value of the "crude" protein. That is an advantage to be attributed to the credit of nitrogenous fertilisers.

CHAPTER 3

*Influence of sulphur of the soil on content of sulphur-containing amino-acids in grass***Importance of amino-acids containing the sulphur atom**

THERE are two sulphur-containing amino-acids, namely methionine and cysteine. By oxidation two molecules of cysteine form a molecule of cystine. (See formulas in Fig. 2 on p. 6.)

It seems that in grass and various forage plants the sulphur-containing amino-acids constitute a limiting factor in the biological value, that is to say, in the "actual nutritional" value of the protein of the plant.

Possible deficiency of sulphur

When basic slag, potassium chloride and nitrate of calcium are regularly applied to grassland or cultivated crops, sulphur is omitted and there is a risk that after some years there will be a deficiency of sulphur.

We will show that this impoverishment of the soil in sulphur will exercise a marked influence on the composition of the nitrogenous matter of the plant.

The content of methionine in lucerne reaches a maximum

Table 4 on p. 11 shows the variations in the methionine content of lucerne as a function of the sulphur content of the nutrient solution (335).

We see that in the absence of sulphur in the nutritive solution a gram of lucerne dry matter contains 1.96 mg. of methionine. For 64 parts per million of sulphur in the solution, the lucerne contains the maximum of 5.37 mg. methionine per g. of dry matter or more than double. But if we continue to increase the content of sulphate ions in the solution, the content of methionine in the lucerne diminishes very considerably.

TABLE 4

Influence of sulphate ions on the methionine content of lucerne

Parts per million of sulphur in the nutrient solution	Milligrams of methionine per gram of dry matter
	Lucerne
0	1.96
16	4.50
32	5.01
64	5.37
96	4.61
128	2.70

From Sheldon (335).

This is an example of the universal law of nature: all extreme is harmful; either too much or too little is injurious.

Lucerne which is poorest in nitrogen is richest in methionine and cystine

Table 5, below, shows (371) the variations of the content of the lucerne in:

Nitrogen
Methionine
Cystine

TABLE 5

Influence of the concentration of sulphate ions in the nutrient solution on the content of total nitrogen, cystine and methionine of the lucerne

Concentrations of SO ₄ ions per 1000 parts in the solution	Nitrogen (% of dry matter)	Sulphur (% of dry matter)	Methionine (Mg./g. of N)	Cystine (Mg./g. of N)
0	3.96	0.096	28.1	27.8
1	3.66	0.097	36.3	34.2
3	3.10	0.099	38.3	48.1
9	2.88	0.122	56.4	67.3
27	3.00	0.138	54.1	66.0
81	2.91	0.206	55.9	65.5
Mean	3.25		44.9	51.5

From Tisdale (371).

in relation to the sulphate ion content of the nutrient solution. I extract from the table the following figures:

It will be seen, as in the preceding case, that there is a maximum content of methionine of 56.4 mg. and of cystine 67.3 mg./g. of nitrogen for a concentration of 9 parts per million of sulphate ions in the solution.

When the content of sulphate ions is nil, the contents of methionine and cystine are respectively 28.1 and 27.8 mg., or approximately half.

For concentrations of SO_4 in the nutrient solution higher than 9 parts per million, the methionine and cystine content drops again.

Now it is remarkable that the content in nitrogen of the lucerne is a *minimum*, namely, 2.88 per cent, when the concentration of sulphate ions allows the *maximum* content of sulphur-containing amino-acids.

On the contrary, the nitrogen content is a *maximum*, 3.96 per cent, when this nitrogenous part is the *poorest* in methionine and cystine (no concentration of sulphate ions in the solution).

The usual analysis would have chosen the lucerne with the nitrogenous matter having the lowest nutritional value

Suppose that with the methods actually used for the usual analysis of plants and food one had made a test on the variations of "crude protein" content of lucerne in relation to the application of sulphur, the conclusion of the experiment would have been to advise the application of the quantity of sulphur which furnishes lucerne with the highest content of crude protein which is, according to our actual analytical conception, the best.

In other words, one would choose a lucerne of which the nitrogenous matter had a biological value approximately half that which the necessary application of sulphur would allow.

Methionine as an element in the normal functioning of the organism

This poverty in methionine of the nitrogenous matter of the plant does not show itself merely by a lesser *nutritional* value. That is serious enough, but it is worse—infinately worse—that the health of the animal may be in danger.

The lack of methionine in the plant or in the ration may be one of the causes of certain metabolic troubles in the animal (199, 200, 201).

We know, on the other hand, that methionine can "neutralise" certain unfavourable effects caused by an excess of molybdenum in the plant. Such an excess can have—as we can see later—grave consequences: directly, it can result in diarrhoea; or, indirectly, in copper deficiency, which may, for example, lead to bone fractures or a low fertility of the animal.

We see appearing a first example of the possible outbreak of a disease, namely a disorder of the metabolism of the animal cells, following from a deficiency of the soil in a mineral element, which in this case is sulphur.

of equal importance, however, was the absence of fertilisers in this period of poverty (see p. 211).

CHAPTER 4

The dead mineral matter of the soil creates the vitamin, an element essential to life

Complete fertiliser increases the carotene content of tomatoes and carrots

SCHUPHAN (323) (*) grew tomatoes and carrots on soil receiving either manure (**) alone or manure plus a complete mineral fertiliser (nitrogen, phosphorus, potash). On investigating the influence of these two treatments on the carotene content of the crops it was found (see Table 6, p. 15) that the supplementary dressing of complete fertiliser had increased the carotene content of the tomatoes by 58 per cent and that of the carrots by 23 per cent.

Vitamin A content of blood serum is higher in infants fed on vegetables which have received a complete mineral fertiliser

Schuphan pursued his studies still further, feeding infants on the vegetables produced in the above trial. He established that the vitamin A content of the blood serum of those fed on vegetables grown *with* complete fertiliser dressings was four times as high as that of infants receiving produce grown without such dressings (Table 6, p. 15). The difference was clearly shown in the weight increases of the babies: the daily growth of the group receiving the vegetables grown with mineral fertiliser was 28 per cent higher.

Grass that has received a complete fertiliser dressing is richer in carotene

Reference will be made again later to goitre in the Bavarian village of Riegsee, when it will be seen how local conditions, as a result of the shortage of carotene (provitamin A) in the pasture herbage, assisted the development of a deficiency of vitamin A. A contributory factor

(*) See also p. 191 concerning other functions and works of Schuphan.

(**) Well-rotted in every instance.

TABLE 6

Influence of a complete mineral fertiliser on the carotene content of vegetables and vitamin A content of the blood serum of infants fed on these vegetables

Fertiliser applied to soil	Mg. carotene per 100 g. fresh matter		Mg. Vitamin A per 100 cm. ³ blood serum of infants receiving these vegetables		Weight gain (in g.) per infant per day
	Tomatoes	Carrots	At commencement of experiment	At end of experiment	
Manure	0.42	5.40	0.111	0.114	11.90
Manure + complete mineral fertiliser (NPK)	0.66	6.64	0.101	0.405	15.27

N.B. (1) Carotene or provitamin A is the precursor of vitamin A.

(2) NPK = nitrogen + phosphoric acid + potash.

From Schuphan (323), pp. 101-102.

Table 7, below, shows the carotene contents of three plants on

TABLE 7

Influence of complete mineral fertiliser dressings on the carotene content of three herbage plants

Plant		Carotene content of the fresh plant material (Mathematical unit)	
English name	Latin name	Organic fertiliser	Organic + complete mineral fertiliser
Cocksfoot	<i>Dactylis glomerata</i>	950	1,141
White clover	<i>Trifolium repens</i>	850	1,539
Cow-parsnip	<i>Heracleum</i>	690	735

N.B. (1) Organic fertiliser = manure + liquid manure.

(2) Complete fertiliser = nitrogen + phosphoric acid + potash.

(3) The two fields involved in the experiment were contiguous.

(4) Assessments made in August 1949.

From Haubold (150), p. 174.

two contiguous Riegsee pastures, one of which received only organic fertiliser (manure and liquid manure), the other organic fertiliser *plus* a complete mineral fertiliser. The application of mineral fertiliser has clearly increased the carotene content, almost doubling it in the case of white clover.

Phosphate applied to the soil increases the thiamine content of grain

Scharrer (311) of the Justus Liebig Institute (Giessen, Germany) has studied the influence of various fertilisers on the content of thiamine (*) (vitamin *B*), one of the most important vitamins, since,

TABLE 8

Influence of phosphate application to the soil on the thiamine content of oats and millet

	Thiamine content		Grain yield		Phosphoric acid content	
	Micro-grammes per 100 g.	Relative	G. per pot	Relative	One part per thousand	Relative
(1) Oats (grown on acid sandy soil, very poor in nutritive elements):						
Without fertiliser	357	100	1.48	100	5.56	100
NK	553	155	1.94	131	5.81	105
NK and superphosphate	712	199	30.65	2070	7.20	130
(2) Millet (grown on heavy soil, acid-neutral, poor in phosphorus):						
Without fertiliser	559	100	7.12	100	9.16	100
NK	659	118	15.50	218	9.53	104
NK + basic slag	717	128	19.39	272	8.41	92
NK + superphosphate	768	137	23.62	332	8.92	98

N.B. (1) NK = nitrogen + potassium.
 (2) Phosphoric acid - P₂O₅.
 (3) The trial in question was a pot experiment.
 From Scharrer (311).

according to Terroine's (241) description, "it superintends the utilisation of the glucides". Table 8, above, shows that basic slag or superphosphates (combined with nitrogen and potash) increase by 28-37 per cent the thiamine content of millet grown on heavy soils, while it is as much as doubled in the case of oats grown on a poor, sandy soil.

(*) Also called aneurin. Its phosphoric ester or co-carboxylase plays an important part in the metabolism of the fatty acids and glucides.

The "living" action of phosphoric acid, a "dead" dust

This influence of the phosphoric acid of the soil on the grain's content of one of the most important vitamins is much more important than an increase in the crop's content of phosphoric acid, an element generally measured to estimate the improvement in quality due to the application of phosphatic fertilisers to the soil.

Albrecht has described as the "Ash Mentality" (p. 5) the belief that a mineral element in the soil can exert its influence only on the same mineral element in the plant. We opposed the "living utilization theory", which claims and proves that the "dusts" in the soil control the synthesis of organic matter by the living cell.

Application of phosphate to the soil may considerably increase the thiamine content of the grain without altering its phosphate content

Scharrer's results provide excellent ammunition with which to oppose these two theories. According to Table 8 (p. 16) the application of superphosphate (combined with nitrogen and potash dressings) doubles the thiamine content of oats, whereas the content of phosphoric acid is increased by only 30 per cent. The example of millet is even more striking: application of superphosphate to the soil increases the grain's content of thiamine by 37 per cent, but its content of phosphoric acid *remains the same* and even shows a slight tendency to decrease.

With the analytical methods in current use and the "Ash Mentality" the conclusion in this case would have been that the application of superphosphate to the soil did not improve the quality of the millet even though its higher thiamine content clearly makes it a better product. (*)

Phosphatic fertilisers are among the principal factors governing improved quantity and quality of agricultural products

Application of phosphatic fertilisers to the soil, which is rightly recommended, has effected a considerable improvement in the quality of foodstuffs, whether destined for animals or for Man. Unfortunately it has too often been imagined that this improvement stems

(*) Bains (25) on the other hand, at the Punjab College of Agriculture, India, found that superphosphate, sulphate of ammonia and potassium nitrate did not increase the thiamine content of wheat.

solely from the increased phosphoric acid content of the foodstuffs in question. Scharrer's observations show how infinitely more important the role of phosphatic fertilisers is: they modify fundamental mechanisms of cell metabolism. In the present instance phosphatic fertilisers have improved the functioning of the mechanism for synthesising one of the most important vitamins in human nutrition.

It is often said (174, p.VI): "Phosphorus occupies a unique position in biochemistry. If carbon is the *King*, phosphorus is the *Prime Minister* without whom the king is powerless." Scharrer's experiments admirably illustrate this role of Prime Minister assumed by phosphorus.

Type of potassium fertiliser used determines the increase of thiamine content in the grain resulting from the application of potash

Scharrer (311) has also shown that application of potash to the soil can increase the thiamine (or vitamin B₁) content of millet and peas. But of particular significance is the fact that this result depends on the form of potash used, although the latter hardly affects the grain yield at all. What Table 9, below, shows is, in effect, that under the

TABLE 9

Influence of potassium fertilisers on the thiamine content of millet and peas

Fertiliser applied	Grain yield (1)	Microgrammes of thiamine in 100 g. dry matter
(1) Millet (<i>Panicum Italicum</i>):		
Fertiliser (NP)	3.54	519
Fertiliser (NP) + sulphate of potash	12.37	536
Fertiliser (NP) + muriate of potash	11.88	659
(2) Peas (<i>Pisum arvense</i>):		
Fertiliser (NP)	18.48	574
Fertiliser (NP) + sulphate of potash	22.98	517
Fertiliser (NP) + muriate of potash	22.72	615

N.B. (1) G. per experimental pot.

(2) NP = nitrogen and phosphoric acid.

From Scharrer (311).

particular conditions of pot culture, potash application brings about a considerable increase in yield, which is more or less the same for

both muriate and sulphate of potash. On the other hand, sulphate of potash has no effect worth mentioning on the thiamine content of grain, any increase or decrease being but slight, but *muriate of potash*, remarkably enough, increases the thiamine content of millet by 20 per cent and peas by 7 per cent.

Judicious fertiliser application can increase the thiamine content of human milk

The favourable effect of fertilisers on the thiamine content of foodstuffs is the more interesting, since thiamine, as stated above, is one of the most important vitamins. But another fundamental fact has made its appearance in recent years.

Although the vitamin B content of cow's milk is more or less constant, the thiamine content of *human* milk is a function of the amount of this vitamin contained in the diet. This fact has been confirmed by many investigations (192, 217). One of the most interesting studies, carried out in India in 1957, showed (290) that the inclusion of thiamine in the diet could increase the thiamine content of human milk by 50 per cent.

The objection may be raised that India is a country where polished rice, which is deficient in thiamine (see p. 180), is a main feature of the diet. But it is well to remember that white flour contains but half as much thiamine as whole-meal flour (170, p. 53). It is important to see that the foodstuffs one consumes contain as much of this vitamin as possible.

Effect of the mineral elements of the soil on plant enzyme activity

The more progress that is made in biochemistry, the more vitamins appear as being almost always constituent elements of enzymes, and therefore indispensable to the proper functioning of the latter. Mineral elements, moreover, can directly influence the enzyme content of plants. As the immense part played by catalase (*) in microbial diseases and cancer will frequently be referred to in the following pages, an example of the influence of a mineral element in the soil on the catalase of plants may be of interest here.

Table 10 (p. 20) shows that, by adding suitable amounts of iron to the nutrient solution, the catalase activity of a plant can be multiplied by five—evidence of the influence of the "dusts" of the soil on the activity of the enzymes that regulate the functioning of the living cell.

(*) For the definition and functions of catalase, see p. 112.

TABLE 10

Influence of iron in the nutrient solution on the catalase content of sunflowers

P.p.m. iron in the solution	Iron (p.p.m.) in dry matter	Nitrogen (N) in dry matter as %	Catalase activity in dry matter
0.001	76.5	3.18	4.14
0.250	169.5	4.39	17.81
10.000	191.0	4.88	20.69

N.B. Catalase activity is measured with a mathematic unit.

From Weinstein and Robbins (406).

According to their correct or incorrect use, mineral fertilisers improve or reduce the quality of agricultural products

These few examples illustrate the *beneficial* influence that mineral fertilisers in the soil can exert on the quality of the plant. What must be stressed is that mineral fertilisers have not only considerably increased the yields of agricultural crops: if correctly used, they can clearly improve the quality. But, it must likewise be remembered that the same fertilisers incorrectly applied *reduce* the quality of the produce.

Schuphan's study (324, pp. 81-82) on spinach demonstrates very well the twofold action that mineral fertilisers can have on the quality of a plant. Spinach contains a substance—oxalic acid—injurious to human health. Dressings of nitrate *increase* the oxalic acid content, while dressings of potash *decrease* it. Obviously, therefore, the application of nitrate alone to spinach will lower its quality, and may even have disastrous results. However, the *injurious* effect of nitrate can be eliminated by the *favourable* effect of the application of judicious quantities of potassium which will increase the yield of the spinach, at the same time improving its quality.

CHAPTER 5

The soil makes the animal and the man

From the soil to the man via the plant and the animal

As I have stated at the beginning, our ancestors recognised districts where a special soil type in certain climatic conditions resulted in a breed of animal with marked qualities.

If we define the influence of the soil on the animal, we can make the generalisation

the soil makes the grass
the grass makes the animal
and finally
the soil makes the man.

It has just been shown that the elements of the soil modify fundamentally the composition of the "crude" protein of the grass and, as a result, enables a different animal to be evolved.

We will now try to relate the modification of this so-called protein of the grass to the gain in weight and the general appearance of the animal.

The application of mineral fertilisers to the soil makes possible a higher gain in weight of the animal

Table 11 (p. 22) enables a comparison to be made between the composition of lucerne and the gains in weight of rabbits fed with this lucerne.

We see (335) that the application of magnesium and trace elements slightly lowers the nitrogen content of the lucerne and increases significantly its content of tryptophan and methionine.

This improvement of the "crude" protein, due to the application of mineral fertilisers to the soil, results in improving the nutritional value of the lucerne for rabbits. Those fed lucerne grown on the control soil make a gain of only 740 g. At the same time the rabbits fed with lucerne produced on the improved soil make a gain of 849 g. or 15 per cent more. Now this 15 per cent greater gain in a steer often represents the profit on the animal.

This gain has been obtained thanks to the application of complete mineral fertilisers to the soil. Once again it is shown that mineral fertilisers, *correctly* applied, can be a source of health and profit.

TABLE 11

Influence of trace elements in the soil on weight gains in rabbits

	Soil	
	Control	Application of magnesium and trace elements
	Contents of a gram of dry matter of lucerne grown on the corresponding soil	
Milligrams of:		
Nitrogen	31.2	30.5
Tryptophan	1.86	2.52
Methionine	4.54	5.44
Mean weight gain in grams of rabbits fed with corresponding lucernes	740	849

From Sheldon (335)

The same plant grown on five Missouri soils produces very different rabbits

Table 12 on p. 23 shows that five different soils in Missouri provide a lespedeza (Korean legume) containing in each case different proportion of amino-acids. It can also be seen that the application of fertilisers modifies, and, in certain cases, improves the composition of lespedeza in amino-acids. Fig. 4 (facing p. 22) (1,4) shows the appearance of rabbits produced on the five soils (not treated) of Missouri. A considerable difference in appearance and in size between these different rabbits can be noticed.

For certain soils the application of mineral fertilisers has resulted in a considerable improvement in appearance and size (animals on the right).

We have in this a good example of the statement "the soil makes the animal". We have besides a new proof that the *judicious* use of mineral fertilisers can bring a considerable improvement in the animal.

An unusual experiment carried out in that immense human laboratory, India, provides further evidence that soil makes Man.

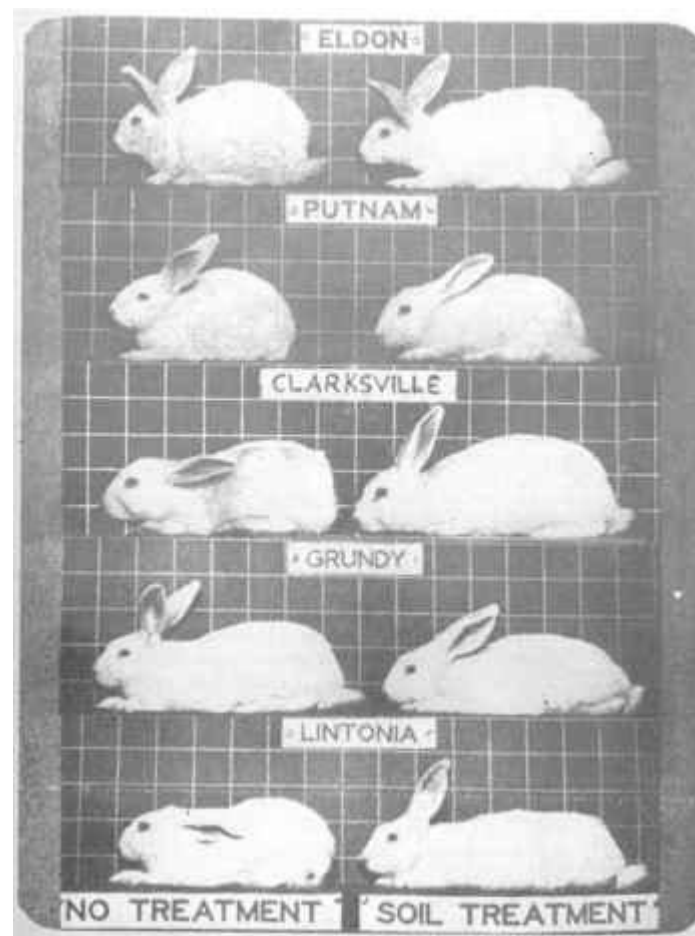


FIG. 4. Different development of rabbits which have consumed lespedeza grown on different soils, with or without fertiliser applications.

No treatment = no fertiliser dressing.

Soil treatment = fertiliser applied to the soil.

The names indicate the soils.

See Table 12 on page 23 showing the amino-acid composition of the lespedezas consumed.

From Albrecht (1, 4).

DIET AND PHYSIQUE OF INDIAN RACES.

The soil makes the animal and the man

23

TABLE 12

Contents of certain amino-acids in the protein of a leguminous forage (lespedeza) in relation to the soil where the plant is grown and to the application of fertilisers to the soil

Type of soil	Tryptophan		Lysine		Methionine	
	Un-treated soil	Treated	Un-treated soil	Treated	Un-treated soil	Treated
Eldon	0.205	0.294	0.943	0.992	0.086	0.092
Lintonia	0.181	0.279	0.878	0.872	0.077	0.077
Putnam	0.227	0.244	1.007	0.894	0.080	0.084
Grundy	0.195	0.196	0.938	0.797	0.082	0.079
Clarksville	0.215	0.258	0.870	0.930	0.074	0.076

See the photograph facing p. 23, which shows the appearance of the rabbits which had consumed the different lespedezas.

From Albrecht (1, 4).

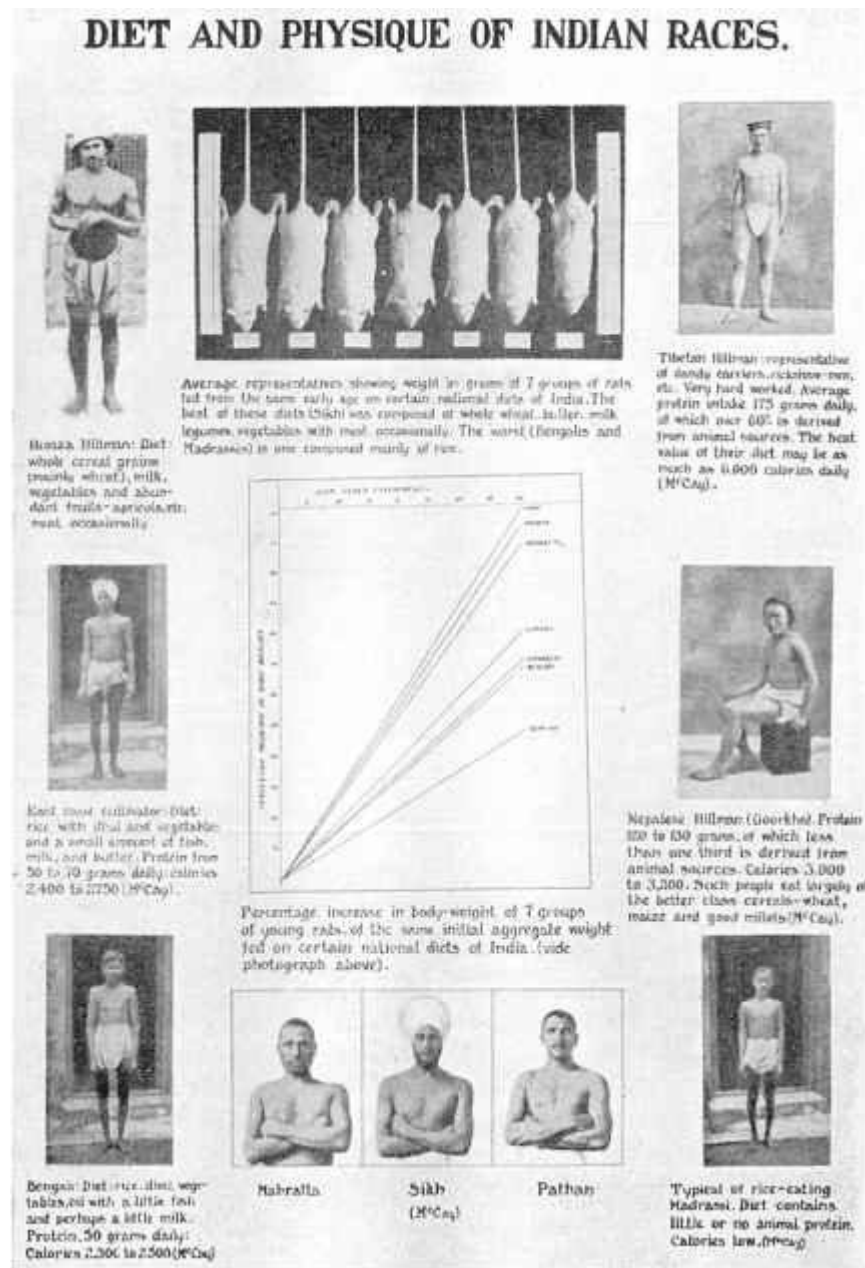
A great scientist's nutritional experiments

Sir Robert McCarrison worked in India for thirty years as Head of the Nutrition Research Services and finally as director of the Pasteur Institute at Coonor in Southern India. In this enormous country of many peoples and diverse soils McCarrison carried out innumerable studies concerned with the influence of soil and nutrition on Man. Only one of these will be referred to here, providing a striking illustration of the relationship between soil, nutrition and the human being.

The same feeding makes both rats and men strong or weak

The races constituting the 400 million inhabitants of India differ greatly in their physical characteristics. Many of them have sometimes been settled on the same soil for centuries, with the result that the cumulative effects of the soil (and the foodstuffs it produces) have been able to make themselves clearly felt on the characteristics of the race in question.

McCarrison had the idea of feeding rats with the food eaten by these different peoples. Fig. 5 (facing p. 23) is an original photograph taken by him (237, p. 24) and shows the physical appearance of nine different races. Seven groups of identical rats were fed on the same rations



as seven of the nine races represented. The graph in the middle of Fig. 5 shows the mean percentage increase in the weight of the rats of the various groups on the twentieth day of the experiment. A photograph of the rats, arranged in the same order, is shown in the top centre. From their weight and growth it will be seen that the rats, in terms of the food they have received, are grouped as follows: Sikh, Pathan, Maharatta, Gurkha, Kanarese, Bengal and Madrassi.

One has only to look at the first and last of the peoples in this classification to see the vigour of the Sikh (*bottom centre*) compared with the miserable appearance of a Madrassi (*bottom right*).

This helps one to understand the ancient proverb, "The same soil makes both corn and man", which, stated in more scientific, but unfortunately more prosaic, modern terms would read, "Animals and men are the biochemical photograph of the soil."

CHAPTER 6

Man and the animal, not the chemist, are the supreme judges of agronomic methods

Limitations of the chemical analysis of foodstuffs, plants and soil

ON the basis of the examples given above, attention should be drawn at this point to a fundamental factor: the insufficiency of current methods of chemical analysis.

It has been, and still is, imagined that chemical analysis as it is carried out today reveals the true nature of soils and foodstuffs, and will unfailingly provide warning of the dangers which might result from the application of a deficient agronomic method. This is a great illusion.

To turn to foodstuffs analysis: it must be remembered, and stressed, that what is determined are "analytical groups" and not simple chemical constituents. It might even be said that these groups are "mere creations of the mind of the chemist". What we call "crude fibre" is in fact only the part that is insoluble under conditions determined by the analysis. The outstanding presumption in the analysis of foodstuffs is, perhaps, the labelling as protein of what is only nitrogen (estimated by the Kjeldahl method) multiplied by 6.20. Sometimes (but not always) the analyst adds the qualification "crude" to the word protein. As has already been said (388, p. 96): "Such protein is only 'crude' protein and certainly one all too crude to be taken as the basis for complete nutrition."

So, when a chemist worthy of the name, the 1952 Nobel prize winner in Chemistry, R. L. M. Synge (365), considers the methods of analysis of foods and grass he is simply shocked. This great scientist makes the comment: "It is indeed a great presumption to give advice to a farmer on the nutrition of his animals on the basis of the results of tests on nitrogen content by the Kjeldahl method."

It has been demonstrated (pp. 11-12) that in thus confusing nitrogen and protein there was a danger of selecting a plant with *true* protein of inferior biological value.

The mineral element of food is not completely assimilable

As far as mineral elements of food and plants are concerned, we analyse only the total of the elements, which gives us no information on the proportion assimilable. In order to get accurate knowledge on the "efficiency" of these mineral elements, it would be necessary to know the mineral or organic combinations under which they are found, the proportion of the different mineral elements among themselves, etc.

Chemical analysis of the soil indicates merely the total of the elements

Routine chemical analysis of soils, that is to say, that practised in 99 per cent of cases, can provide only very limited information; worse still, it can be responsible for serious errors.

This analysis in the case of the soil—as in the case of food—can indicate precisely only the *total* of an element; it cannot give us information on the availability of this element.

Besides, ordinary soil analysis concerns only certain elements. In a soil sample to be analysed the laboratory tells you that it contains sufficient phosphate and calcium, and yet the animals on these soils will be attacked by rickets and bone fractures because the soil is deficient in copper—of this I shall quote an example from Florida (pp. 32-34). The usual soil analyses do not deal with copper and if that analysis were made it would concern only the *total* copper.

The analysis of available copper of the soil—even if it were possible (and it is not possible) to carry it out in a precise manner—would still give no information. The soil can contain sufficient available copper and yet we may have deficiencies in copper in the animal if the soil contains an excess of molybdenum, which is antagonistic to copper. Such analysis for all the available trace-elements of the soil would cost hundreds of pounds and give little information.

The biological test alone can enlighten us

The biological test with the animal, whether it is with rats, rabbits, guinea pigs or sheep, shows us at a glance the global influence of *all* the elements of the soil and of the plant on the animal organism.

In other words, the biological test gives us the influence of all the elements of the soil through the plant on the metabolism of the animal cell.

Man and the animal, not the chemist, are the supreme judges 27

Lady Eve Balfour (26) contributes to this subject the statements of Albrecht of the University of Missouri:

"He says that, for assaying food values, no instrument as yet invented by man is so delicate and so perfect as the living organism. That is why he is not content with any analytical methods for determining quality *that have not been confirmed by results of actual feeding tests with animals.*"

The chemist and the animal are not in agreement

I think that a personal reminiscence and a striking formula will help to show that present ideas on chemical analysis do not give satisfaction—to the animal.

At the beginning of 1957 the British Society of Animal Production invited me to give a talk during which I discussed ideas similar to those expressed here.

I underlined the great weakness and even the dangers of our actual methods of analysis of feeds and in particular of grass.

Professor M. McG. Cooper, Dean of Agriculture, the University of Durham, in the course of the discussion—the day following my address—repeated my point of view through the following formula:

"As M. Voisin has forcibly explained to us, a herbage which appears ideal to the chemist as judged by his analysis is not necessarily ideal for the cow."

It would be difficult to put more clearly my view as a biochemist and farmer.

Raising the status of chemical analysis

Chemical analysis, thanks to the biological test, may be raised in status.

In the soil, in the plant or in a living organ chemical analysis can indicate in a precise manner—as I have already said—only the sum *total* of the element.

But when one measures this element in an organ which is truly "indicative" this analysis can be very valuable. We may, for example, analyse the manganese content of the ovary in an autopsy (see p. 69) or the copper content of the liver by biopsy. (*) (See p. 40.) We will learn thus a thousand times more about the manganese and copper status of the soil than by soil analysis.

Analysis with the help of the biological test can take more refined forms. We may determine, for example, the activity of a special

(*) Taking away a fragment of an organ from a living being.

enzyme in the blood, as, for example, catalase, and we can deduce valuable information on certain deficiencies of the soil or of nutrition (see p. 114).

Raising the status of chemical analysis is a primary condition of progress in the sciences of life. Only when the present conceptions of such analysis have been modified will the influence of soil and feeding on cell metabolism in animals and in Man be completely revealed. Such a revelation, and the knowledge it will bring in its train, is essential to the future creation of an efficient "protective" medicine.

CHAPTER 7

Deficiency of copper in the soil disturbs the metabolism of certain cells in the animal

A soil deficiency modifies the metabolism of the cells in wool formation

WE are going to show how the mineral elements of the soil can modify the metabolism of certain cells of the *animal* itself.

It has been observed in Australia that, on the soils of certain districts, wool loses its crimp and takes on what is called a "steely" appearance. The production per sheep is besides markedly diminished and the strength of the fibre is much lower.

It has been shown that this arises from a copper deficiency and that the application of sulphate of copper to the soil remedies the defect.

One can definitely show that in the case of individual sheep the addition of a supplement of copper in the ration, or intravenous injection of an isotonic (*) solution containing copper, suppresses the faults in the wool.

Deranged mechanism of keratinisation

The formation of wool in the follicle can be considered (in a simplified manner) as the transformation of pre-keratin protein into keratin (**) protein.

From the biochemical point of view, this transformation is effected by the closure of the sulphydryls (-SH) of the pre-keratin to the disulphide (-S-S-) linkages of keratin (see Fig. 3 on p. 6).

The disulphide groups form cross-linkages which are considered indispensable to give wool its physical characteristics, in particular its crimp.

Now it is possible (226), thanks to a specific histochemical reaction, to follow in the follicle the transformation of the sulphydryls into

(*) Isotonic is the state of liquids having the same osmotic pressure.

(**) Keratin is scleroprotein characteristic of horn tissue, hair, wool, feathers, etc.

disulphides. In particular alkaline nitroprusside gives a deep purple reaction with the sulphhydryls, but not with the disulphide groups.

When this reagent is applied to the base of a normal fibre (pulled out from the follicle) the colour reaction extends for a length of about 100 microns. On the contrary, with the wool of a sheep which has been raised on a soil deficient in copper the colour reaction extends over a length ten times as great—1000 microns. This shows that the transformation of sulphhydryls into disulphide groups is made *imperfectly and slowly*.

The copper supplement in the ration re-established within four hours normal metabolism in the follicle

When a sheep suffering from copper deficiency receives a supplement of copper—either orally or by intravenous injection—about *four hours* afterwards the purple colour with nitroprusside assumes its normal length of 100 microns (34).

This shows that the enzymes with copper, four hours after oral administration of copper, catalyse the oxidative closure of the sulphhydryls and that keratinisation proceeds again normally. The wool which emerges subsequently from the follicle has its crimp and its other physical characteristics normal. Unfortunately, the wool already formed, that is to say, having emerged from the follicle, has suffered an *irreversible* lesion, and the application of copper in the ration cannot improve it (57).

Damage to the soil creates in the animal proteins which are of pathological character

This example of disturbance of the mechanism of keratinisation arising from a deficiency in the soil shows us well how an unhealthy soil can produce in the animal or in man an unhealthy *protein*.

As we will see later, the application of unbalanced fertilisers can produce in the soil many deficiencies, and in particular a deficiency of copper.

Therefore, if our farming methods are injurious to the soil, we injure as well the animal and human organism, because we create therein proteins of a *pathological* character which are manifested in the cell through defective metabolic mechanisms and permit the cell to be attacked by bacterial or virus infections.

Further, these deranged cells age more rapidly or may cause the appearance of these diseases of metabolism which are called cancer or thrombosis.

Copper and sterility

There are many causes of sterility in animals. If we leave aside microbial infections, nutrition is one of the principal factors.

I would like to examine three causes of sterility, namely, copper, manganese and oestrogens.

For the moment, I will consider only the relationship between copper deficiency and sterility in cows. At the Veterinary Research Centre of Weybridge, Hignett (157) has observed that districts with copper deficiency are increasing in Great Britain, and that he has never met a herd of cows suffering from copper deficiency in which the percentage of fertility was satisfactory. He has shown, among other things, that in such herds the simple administration of copper to the animals led to a spectacular improvement in reproductive efficiency.(*)

I have (**) very often obtained in this way a good result in treating with copper cows in difficulty with pregnancy.

(*) *Hignett's Doses*. The doses utilised by Hignett with cows were the following:

(a) 1 g. of sulphate of copper administered orally for a duration of one month,

or

(b) A single intravenous injection of 100/300 c.c. of an isotonic solution containing 1 mg. of copper per c.c.

(**) *Voisin's Doses*. Personally, I have utilised a dose of 2 g. of copper sulphate per day and per cow in the following manner:

When a cow comes into heat for the third time and is not affected by cysts or infectious diseases, etc., I give, immediately the heat is observed, a drench of 2 g. of sulphate of copper dissolved in a litre of water. The cow is not served until eight hours after this dose.

My reasoning is as follows: in the case of keratinisation, four hours after oral administration the enzymes with copper function normally. I hope that it will be the same for the enzymes with copper playing a role in reproduction, if they play such a rôle.

During the twenty following days I continue to give each day to the cow 2 g. of sulphate of copper orally.

CHAPTER 8

Copper considered as a cement to repair bones

The Everglades pastures of Florida

THERE exists in Florida, around Lake Okeechobee, a district called the Everglades covering 700,000 acres of grassland on soils *very rich in organic matter, relatively little decomposed*.

Thanks to the very mild climate of Florida, it is possible to graze all the year round. The stocking in spring is about four beasts to the acre, and in winter a little less than one beast per 2 acres.

The animals are therefore fed exclusively all the year round with the grass which they graze. This enables observations to be made in a *complete and striking* manner on the influence that the soil can exert on the animal.

The soil was sufficiently rich in phosphorus and calcium, and yet bone fractures were frequent

Unfortunately livestock farming was rendered very difficult by frequent bone fractures, which were observed in cattle grazing these Everglades pastures. These animals showed all the signs of rickets.

One immediately thought of a lack of phosphorus and calcium in the soil and in the grass, but all analyses confirmed that there was no such deficiency (85, 195).

It was then discovered that it was a question of a copper deficiency, for the application to the soil or the oral administration of that metal prevented the occurrences.

This further explains my ideas about the limits of our methods of chemical analysis (see pp. 25-28) and the necessity of the real biological test; the normal analysis of the soil and of the grass indicated contents largely adequate in phosphorus and calcium and yet the animals were stricken with rickets and osteomalacia.(*).

In fact, even refined chemical analysis does not allow measurement

(*) General softening of bones.

to be made of the quantity of available copper in the soil, and this determination, in a manner which is yet only approximate, can be made only by an analysis which is in fact a microbiological test. A micro-organism called "*Aspergillus Niger*" is grown on a preparation of the soil. But this long and complicated analysis does not give very much information, while the biological test which consists in giving copper to the animals of the Everglades was truly spectacular.

Copper repairs the broken bones

I think it useful, among many experiments made in the Everglades, to report one in some detail: a calf grazing had a fracture of both shoulder-blades, and the vertebral column seemed to sink between the fractured shoulder-blades. The calf was dosed with 3 g. of sulphate of copper every ten days. There was a rapid improvement. The shoulder-blades united again and the vertebral column assumed an almost normal position. Further, the staring coat again became glossy.

As long as this calf received copper he made normal growth and his health remained excellent.

After six months the feeding with copper was stopped. The calf again assumed a miserable appearance and developed a fracture of the humerus. The administration of copper was resumed and—a remarkable fact—the fracture knit rapidly. Once more the calf took on a healthy appearance and made normal gains.

Copper permits the bone cell to "organise" phosphorus and calcium

In other words, the metabolism of bone cells is disturbed by the deficiency of copper (32), but in this case at least in a *reversible* manner. I cannot pursue here the relationships between copper in the ration and the alkaline phosphatase of the bone which plays a fundamental role in the metabolism of bone cells.

It would be equally desirable to examine the influence of copper in the functioning of the parathyroid glands. I can merely draw attention to these important points.

We can say simply that ordinary rickets is due to an insufficient deposit of phosphorus and (or) calcium in the bone cells because an *insufficient* amount of these two building materials is available for them. But the same rickets is produced in the presence of *sufficient* quantities of phosphorus and calcium which cannot be constructed and "organised" because of disturbance in the enzyme mechanism

which is controlled by copper. Here we find again the *notion of a trace element as a factor in the construction of living organic matter*.

We may say, taking another analogy, that a mason cannot build the wall (bone cell) either because he lacks bricks (phosphorus and calcium) or because he lacks mortar (enzyme) to keep the bricks together.

The first instance shows the classical rickets due to deficiency in phosphorus and calcium, while in the second, rickets are due to the deficiency of copper, and that is the case of the Everglades.

It is very probable that other elements besides copper are utilised for the construction and metabolism of the bone cell: perhaps it will be discovered in the future that bone fractures can equally be due to other deficiencies.

Indirect deficiency of copper may cause bone fractures

Other forms of copper deficiency may cause bone fractures. The soil and the plant may not lack copper, but they may contain too much molybdenum, which is antagonistic to copper and causes *indirect* deficiency of copper. The problem is rendered still more complicated by the fact that other factors intervene to influence this antagonism.

We recognise today one of these factors, namely, the sulphate ion, and I will emphasise only that in the case of the Everglades the application of sulphate of copper to the pastures (4½ lb./acre [5 kg./ha.] and often more) enables healthy animals to be raised on most of the pastures (195).

But in certain parts of the area—which are, however, relatively small—bone fractures occur fairly often. Recent researches seem to confirm that in these cases an excess of molybdenum in the soil is the cause.

CHAPTER 9

Copper deficiency caused by nitrogenous fertilisers

The country where more nitrogenous fertilisers are applied than anywhere else in the world

IT was stated earlier that we are heading for deficiency diseases and, indeed, that we have already entered that stage, because the yields of our harvests have doubled or trebled. The consequence is that we remove two or three times more elements from the soil and replace in full only a limited number. (Phosphorus, calcium, potassium, etc.)

Holland is the country where for many years very great quantities of nitrogenous fertilisers have been used. It is even perhaps the only country in the world where great quantities of nitrogenous fertilisers are applied *to pastures*, and in certain districts for a considerable time.

It is evident that this use of very heavy dressings of nitrogenous fertilisers for a *considerable* number of years has certain *cumulative* effects, which, in the case of Holland, are disturbing.

Diminution of the copper content of blood serum in the grazing animal

At the Research Centre of Wageningen (Holland) heifers have been put to graze herbage which each year *for sixteen years* had received heavy applications of about 72 and 180 lb./acre [80 and 200 kg./ha.] nitrogenous fertiliser (46, 47).

All these heifers had been suitably fed during the winter, and when put to graze they had per litre of blood serum sufficient copper—0.0 mg.—which is over the limit of safety, which the Dutch scientists estimate to be 0.5 mg. It is to be noted that this figure in normal circumstances can be considered as correct, but that it is a function of many factors. In this case we consider only the question of total copper without taking into account the different forms in which the copper is found in the blood.

Fig. 6 on p. 37 and Table 13 on p. 36 show the variations in the

TABLE 13

Copper content of blood serum of heifers grazing pastures which had received low and high quantities of nitrogen

Number of the heifer	March 31, 1954	July 2, 1954	August 31, 1954	October 6, 1954
Pasture which had received each year (*) 178 lb./acre [200 kg./ha.] of nitrogen				
1	0.60	0.64	0.30	0.14
2	0.86	0.57	0.19	0.14
3	0.99	0.60	0.23	0.10
4	0.83	0.56	0.50	0.21
5	0.84	0.45	0.21	0.08
6	0.70	0.52	0.31	0.18
Mean	0.80	0.56	0.29	0.14
Pasture which had received each year (*) 71 lb./acre [80 kg./ha.] of nitrogen				
7	0.73	0.75	0.72	0.49
8	0.93	0.75	0.79	0.63
9	0.69	0.75	0.58	0.40
10	0.69	0.67	0.50	0.28
11	0.71	0.67	0.68	0.54
Mean	0.79	0.72	0.65	0.47

N.B. The figures indicate milligrams of copper per litre of blood serum.

(*) For 15 years.

From Bosch (47).

copper content of the serum of each of the animals on pastures which had received during the preceding fifteen years heavy applications of nitrogenous fertilisers.

The condensed table set out below—taken from the table above—shows the progressive decline of the copper content of the serum

Date	Lb./acre [kg./ha.] of nitrogen applied annually during fifteen years	
	72 lb./acre [80 kg./ha.]	180 lb./acre [200 kg./ha.]
Milligrams of copper per litre of blood serum		
March 31, 1954	0.79	0.80
July 2, 1954	0.72	0.56
August 31, 1954	0.65	0.29
October 6, 1954	0.47	0.14

Copper deficiency caused by nitrogenous fertilisers 37

in the course of the grazing season, the figures referring to the mean of the respective groups of heifers.

It can be seen that on the pastures which had for fifteen years received 72 lb./acre [80 kg./ha.] of nitrogen each year the copper

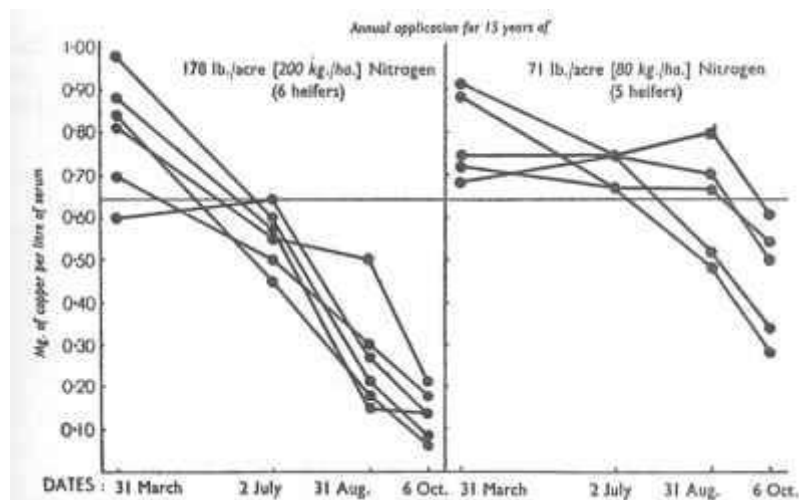


FIG. 6. Annual variations of the copper content of the serum of heifers grazing pastures which had received low and high applications of nitrogen for fifteen years.

From Bosch (46).

(Drawing by Marthe-Rosine Voisin.)

content of the serum is reduced to a mean of 0.47 mg./litre, which is below the limit of safety.

With the pastures which had received 180 lb./acre [200 kg./ha.] of nitrogen the fall in the copper content of the serum is catastrophic, and this content reaches at the end of the season the extremely dangerous figure of a mean of 0.14 mg./litre.

Copper deficiency manifests itself in a fall in the output of the animal

Even if we assume that the impoverishment in copper of the serum is not sufficient to endanger the health of the animal, the output of the animals will be seriously reduced.

The Dutch scientists have prepared diagrams and tables which

show how the production of milk or the gain in weight diminish as the copper content of the blood serum decreases (Fig. 7, below).

Simultaneous reproaches from two directions

The experiments and figures from Bosch seem to show that, without drawing definite conclusions, the employment of heavy dressings of nitrogenous fertilisers for sixteen consecutive years to the pastures caused, through *cumulative* effect, a serious deficiency of copper.

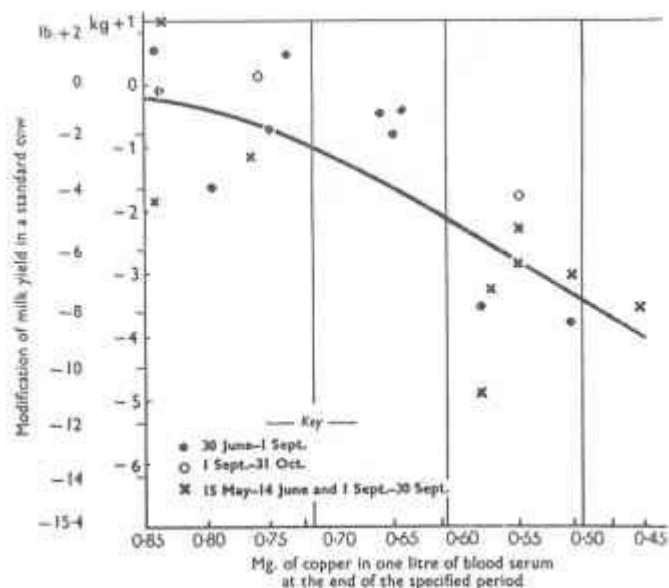


FIG. 7. Average milk yields as a function of the copper content of the blood serum. A diminished copper content of the blood serum brings down milk yields.

From Deijs (87a).

(Drawing by Marthe-Rosine Voisin.)

In drawing attention to this fact one risks hearing on one side a loud cry: "you would have us believe that chemical fertilisers are the cause of all our misfortunes". One also is likely to hear from the other side vehement reproaches: "through foolish statements you seriously injure our commercial interests".

We have as much need of nitrogenous fertilisers as we have of automobiles

I think it necessary to approach this problem, which is extremely serious not only for the animal but also for Man, with a marked sense of realism.

It would be folly to give up the immense and immeasurable benefits conferred by mineral fertilisers. On the other hand, we have not the right to maintain silence, as we do, about the inconveniences and dangers which they present and which, with further research, could be overcome. Silence about "venereal diseases" never cured them: it sometimes even helped to spread them.

If tomorrow it should unfortunately be proved that the exhaust gases of our automobiles are a major factor in the development of cancer of the respiratory tract, we would not suppress our automobiles, for we cannot do without them. We would study methods of absorption, of filtration, of neutralisation, etc., of exhaust gases, and would make it compulsory to equip each automobile with the necessary apparatus.

In the same way, if it is confirmed that the use of very great quantities of nitrogenous fertilisers causes in the *long run* copper deficiencies, with extremely grave consequences, we would not suppress nitrogenous fertilisers, which we need still more than we need automobiles, for it is not at all certain that to give up the use of nitrogenous fertilisers would not result in famine.

It is necessary to extend our conception of basal fertiliser applications

In the present case the remedy for this injurious cumulative effect of nitrogenous fertilisers is extremely simple. It consists merely of applying copper to the soil. Sixty years ago it was found necessary to decide (not, unfortunately, without prolonged controversy) to employ phosphates and potash to "support" nitrogenous fertilisers. The manufacturers of nitrogenous fertilisers in the end advised the simultaneous use of phosphate and potash, for without this support cereals lodged, a phenomenon at once apparent and ruinous to the farmer.

The injurious effects caused by the exhaustion of trace elements in the soil through prolonged use of large quantities of nitrogenous fertilisers are less rapidly visible than in the case of the lodging of cereals, and cause no apparent immediate loss of money. But these effects are all the more serious in as much as they endanger the health of animals and man.

It is a question, therefore, of today extending the conception of basal fertiliser application and of "supporting" nitrogenous fertilisers with many other elements besides phosphoric acid and potash.

We will find the remedies only if we search for them

The problems presented in the replacement of many elements that we remove in *treble quantities without replacing them* are certainly very delicate. The disequilibrium or deficiencies which we create in this way are probably much more complex than in the relatively simple case of copper deficiency.

It is not a question for panic, but the Dutch experiments should receive the attention of the manufacturers of nitrogenous fertilisers all over the world, so that collectively they might study, from now on, the slow, *cumulative* effects of the use of nitrogenous fertilisers. If we do not look for the remedies we will not find them, with the consequent risk of terrible catastrophes, even if they have not already begun, as shown in the statistics of Seekles in Holland.(*)

In Holland more than half the cows have an inadequate copper reserve

Since the copper content of the blood is subject to enormous fluctuations in pathological states (see pp. 120-123 and 129-134), it has been thought that measuring the copper content of the liver, the great copper reserve of the body, would give a better indication of copper deficiency in the animal.

An investigation carried out in Holland into the copper content of the liver of cattle produced the following alarming results. At the Comparative Pathology Congress in Madrid in 1952 Seekles reported that 51 per cent of the cows examined had the very low liver copper content of 5-10 mg./kg. of dry matter, although the normal is around 70 mg. The Dutch scientist concluded: "In the Netherlands the reserve of copper in the liver is therefore *inadequate in MORE THAN HALF the number of cows.*"

One cannot but feel seriously alarmed at the information that in this country, where more nitrogenous fertiliser is applied than anywhere else in the world, particularly to grassland, more than half the cows should be deficient in copper.

(*) Hignett, as seen above (p. 31), found copper deficiency to be increasing in Great Britain also.

CHAPTER 10

From molybdenum in the soil to molybdenum in milk

"Teart" disease

THE word "teart" denotes a disease of cattle which occurs in certain districts of Great Britain, especially in Somerset (112). It is characterised by diarrhoea with faeces of yellow-green colour, full of bubbles, and with an odour of putrefaction.

Red cattle take on a yellowish colour, and black cattle develop a rust-coloured appearance. Sheep are less affected than cattle, although their excrements are very soft. The animals most seriously affected are milking cows and young calves.

Strange characteristics of "teart" disease

This disease presents very curious features:

The diarrhoea has a marked seasonal character.

After the first frosts in the autumn the grass loses its "teart" character.

Hay, made from these pastures, is perfectly healthy and does not cause "teart".

But the most disturbing fact is that animals have often been affected by the disease on a pasture, while on an adjacent pasture other animals were free of it.

It is not a question of a bacterial or parasitic disease

It appeared that bacteria or internal parasites could not be the primary cause of the diarrhoea, for it rapidly disappeared when the animals were removed from the teart pastures.

The drainage of the pastures was satisfactory, and the water consumed by the animals showed no abnormal character.

Ferguson, Lewis and Watson then decided to look for a trace element in abnormal quantity (too low or too high) in the grass (112).

High molybdenum content of teart pastures

Spectrographic examination showed a constant difference between the teart and non-teart grass, the molybdenum content being much higher in the teart grass. The mean molybdenum content of the grass in a dozen localities affected by teart diarrhoea was 33 parts per million in the dry matter in 1937 and 38 parts in 1938. The molybdenum content of the grass from seven neighbouring non-teart localities was respectively for these two years from 5 to 4 parts per million.

TABLE 14

Molybdenum content of grass from teart and non-teart pastures in different localities

Year	Locality	Pasture type		
		Teart	Medium teart	Non-teart
1937	W	51	—	4
	Go	14	—	5
	Gr	—	14	—
	Go	25	—	12
	D	—	12	—
	K	20	—	4
	Cd	52	—	4
	Wh	40	—	6
	M	30	—	—
	P	30	—	3
	H	—	24	—
	Lu	—	13	—
1938	W	59	—	4
	Co	49	—	4
	K	18	—	5
	Wh	27	—	4
Mean, 1937 1938		33 38	16 —	5 4

N.B. The figures show the content in parts per million of dry matter.

From Ferguson (112).

Table 14, above, shows in detail the figures for each of these localities. It has been shown that in Great Britain it was rare for the molybdenum content of grass to exceed 7 parts per million, except for some very exceptional cases, where 20 parts per million are found.

Molybdenum seems to be the cause of teart

After the high molybdenum content of grass was proved, it was natural to suppose that this element was the cause of the teart diarrhoea. This idea seemed to be rapidly confirmed, for when molybdate of ammonium or sodium was administered orally to the animals most of them were affected with diarrhoea, although the degree of this diarrhoea varied with the animal.

Furthermore, when sodium molybdate was applied as a *fertiliser* to the non-teart pastures, it was found that:

- (1) The molybdenum content of the grass increased considerably.
- (2) Cattle grazing this grass were affected with teart diarrhoea.

The soil of teart pastures is abnormally rich in total molybdenum

This experiment led to the idea that the soil of teart pastures was too rich in molybdenum, and this was confirmed by analysis, at least as far as *total* molybdenum was concerned.

The soils of teart pastures contain in the superficial layer about 20-100 parts per million, and the soils are either neutral or alkaline (112). In contrast, soils of non-teart pastures contain only 1-4 parts per million of molybdenum.

According to Ferguson, the molybdenum seems to be concentrated in the clayey portion of the upper part of the lias.(*). The chalk itself contains little molybdenum.

Seasonal changes in the molybdenum content of the grass

These first observations seemed, then, to confirm the hypothesis that too high a molybdenum content in the grass was the cause of teart diarrhoea. But there still remained certain points to clarify.

The diarrhoea had a very marked seasonal character, and was especially severe at the beginning and at the end of the season.

The *seasonal* variation in the molybdenum content of the grass was then ascertained. It was found that there are two seasonal maxima, which vary according to the climatic conditions of the year, but occur, in general, in May-June and in August-September.

(*) Layers of the lower part of the Jurassic formation. An old term of English quarriers signifying regular strata of hard chalk.

Grass subjected to a frost or as hay no longer causes teart disease

As already stated, grass which has been subjected to a frost, even a light frost, does not cause teart disease. Neither does hay from grass grown on these pastures cause the disease.

TABLE 15

Percentage of the molybdenum present which is soluble in water, in normal fresh grass, in fresh grass which has been subjected to frost and in hay

Month of the year	Nature of the grass	Percentage of molybdenum present, which is soluble in water
<i>Pasture from locality W</i>		
July	Fresh grass	83
September	Fresh grass	71
	Standing grass, half dead	58
June	Hay	38
December	Grass that had been subjected to frost	13
<i>Pasture from locality K</i>		
December	Fresh Grass	56
	Grass that had been subjected to frost	4

From Ferguson (112).

Ferguson (112) thought that the frost or the hay-making process rendered the molybdenum insoluble in water, and consequently not capable of being assimilated by the animal. This was confirmed by measurements, the results of which are shown in Table 15 above.

We see, for example, that for the locality K, 56 per cent of the molybdenum in fresh grass is soluble, while after a frost there is no more than 4 per cent of this molybdenum soluble in water.

The total mineral element of the grass is of little significance

It is again apparent that the *total* content of the grass (or of any food) in a mineral element has little significance. The fresh grass and the frosted grass had exactly the same *total* molybdenum content, but in the one 56 per cent was *soluble* in water, as against 4 per cent in the other. The difference resulted in the first being extremely dangerous, while the second was harmless.

Therapeutics of teart diarrhoea

As it is known that copper and molybdenum are antagonistic, the animals were treated with copper, orally or intravenously (112). In addition, fertilisers containing copper were applied to the teart pastures. These treatments of the animal and the soil proved in most cases to be effective, but, however, not always. The exceptional cases led to a closer study of the copper-molybdenum antagonism, which is of great complexity, as already stated.

Higher content of molybdenum of the grass of young leys in the first year

I have referred in my book *Grass Productivity* (388) to the fact that in the grass of a young ley there is a disequilibrium in mineral elements (Verdeyen) and that herds of cows grazing such leys *exclusively* have a low fertility rate (Hignett) (156).

On the other hand, it is known that too high a molybdenum content in the food may cause lesions of the reproductive organs, resulting in a more or less marked degree of sterility.

In the University of California (28) it has been shown that the grass of a young ley had a much higher molybdenum content in the

TABLE 16

Influence of the age of the ley on the molybdenum content of plants

Designation of field	A		B		C		F		H	
Age of ley (years)	1	2	1	2	1	3	1	3	1	2
Plant	Mg. of molybdenum per kg. of dry matter									
Ladino white clover	103	20			32	8	50	30		
Lucerne	21	6	17	7	14	5	17	8	30	15
Birdsfoot trefoil	105	48	90	67	55	26				
White sweet clover			63	50			90	50		
Rye-grass	20	7			7	3				

From Barshad (28).

first year than in the *following* years. This is shown in Table 16, above, from which it is seen that in the second year the molybdenum content of the plant is sometimes three to five times lower than that of the same plant in the first year of the ley.

The question arises as to whether this abnormally high molybdenum content of the grass of a very young ley may be a contributory cause of the sterility noticed by Hignett.

We know in fact that molybdenum is antagonistic to copper, and we have already seen that copper deficiency may lead to sterility in cows.

Enormous variations in the molybdenum content of milk

Milk is very poor in copper, and it is extremely difficult to increase appreciably the copper content of milk by increasing the copper content of the food.

On the other hand, if the molybdenum in the ration is raised, the molybdenum content of the milk of the cow can be considerably increased, and even sometimes be multiplied by *ten* (73).

We may, therefore, accept the fact that cows grazing on soils with a high molybdenum content, or fed on the grass of very young leys, will give a milk with a relatively high content of molybdenum.

The question arises as to the effect on the baby, the man or the calf of this milk with such a high molybdenum content.

CHAPTER 11

Disturbance of the equilibrium of the soil similarly disturbs the equilibrium of the blood

"Luxury consumption" of potash by the plant

WHEN potash is applied to grass (or to any other forage plant) it gorges itself immediately and indulges in what the Americans call "luxury consumption". The result is that following the application of potash fertiliser there is an enormous increase, of relatively short duration, of the potash content of the plant.

For example, in the course of American experiments, a white clover, on the soil which was being studied, had a content of 1.2 per cent of potassium in the dry matter. Substantial applications of potash fertiliser increased this content to 3 and even 4 per cent, that is to say, more than treble (173, p. 60, and 384, pp. 51-53).

The application of potassic fertiliser to the soil may unbalance the potassium-magnesium relation of the grass

The application of potassic fertilisers to the soil has the effect of tending to diminish at the same time to a small extent the quantities of magnesium and calcium absorbed. As Table 17 (p. 48) from Klapp (189) shows, the result is a mineral disequilibrium of the plant, the ratio $\frac{K_2O}{CaO + MgO}$ being increased by 60 per cent. Some or the consequences of this disequilibrium will be described.

The figures contained in Table 18 on p. 48 were given (393) at the Potassium Symposium organised in 1954 by the International Potash Institute. The study from which the figures are derived was undertaken in order to compare the yields obtained and the increase in the potassium content of the grass with increasing rates of potassium fertiliser. The author concluded that when the dry matter of the grass reached a content of 2.99 per cent potassium, there was no point in

TABLE 17

Influence of potash fertiliser on the composition of grass

	Without fertilisers	With fertiliser	
		P ₂ O ₅ + K ₂ O	N + P ₂ O ₅ + K ₂ O
	Relative variations		
Ash	100	109	105
K ₂ O	100	135	125
CaO	100	100	90
MgO	100	90	78
$\frac{K_2O}{CaO + MgO}$	0.50	0.71	0.82

From Klapp (189).

TABLE 18

Influence of potash application to the soil on the ratio of potassium to magnesium in the plant

Potash (K ₂ O) applied lb./acre [kg./ha.]	Grass produced lb./acre [kg./ha.]	Composition of grass		
		Potas- sium, K (%)	Mag- nesium, Mg (%)	K/Mg
0	6,900 [7,620]	1.00	0.85	1.18
57 [63]	5,500 [6,100]	1.15	0.72	1.60
115 [127]	16,300 [18,100]	1.16	0.62	1.88
230 [254]	21,000 [23,000]	2.99	0.41	7.30
570 [635]	17,600 [19,500]	3.66	0.30	12.10

N.B. (1) Although not stated, percentages of potassium and magnesium are related to the dry matter.

(2) The K/Mg ratio was calculated by the author and does not appear in the original article.

From Walsh (393).

applying supplementary dressings of potassium fertilisers, for the yield not only did not increase, it diminished. This diminution in yield he attributes to the fact that, beyond this point, supplementary applications of potassium fertiliser give rise to symptoms of magnesium deficiency in the plant.

It would have been very interesting, from my own point of view, if he had studied the influence of potash on magnesium deficiency, not only *in plants* but also in the *animal* consuming the plants.

The danger becomes even more evident if, instead of examining the two mineral elements separately, one studies their ratio. It will be seen that potassium fertilisers have multiplied the potassium/magnesium ratio by 7.00.

The many causes of grass tetany

Different aspects of grass tetany (*) were studied in *Grass Productivity* (388, pp. 123-128). There are many causes which may result in an outbreak of grass tetany, but they all seem to amount to the same thing, namely an ionic disequilibrium, with the result that in the blood, relative to the magnesium ions, there is too strong a concentration of potassium ions, which causes a paralysing action on the bulbar respiratory centre.(**)

Dutch scientists have studied statistically the percentage of cases of grass tetany as a function of the ratio in the grass

$$\frac{K}{Ca + Mg} \quad \text{or} \quad \frac{\text{Potassium}}{\text{Calcium} + \text{Magnesium}}$$

a ratio which increases with the application of potash fertilisers to the herbage.

Kemp's (185) Table 19 on p. 50 shows that when this ratio is less than 1.40 grass tetany is unknown. For ratios between 1.80 and 2.60 the percentage of tetany varies from 2 to 5, when the ratio exceeds 3.40 the percentage of animals affected by tetany exceeds the enormous figure of 17.

Excessive applications of potash fertilisers to the soil have ultimately destroyed the equilibrium of the mineral elements of the blood

It must be emphasised that our excessive application of potash to the soil has caused a disequilibrium in the *soil*, resulting finally (through the intermediary of the grass) in a disequilibrium in the elements of the *blood* of the animal.

(*) Grass tetany is characterised by sudden paralysis, reminiscent of that found with milk fever. It has developed greatly in recent years in areas where ploughing up of permanent pasture has been systematically practised. An intravenous injection of magnesium salt often produces a spectacular recovery.

(**) A question which, to me, seems not yet to have been dealt with, is to know if this disequilibrium between potassium and magnesium could affect the parathyroid glands, the removal of which causes convulsions and paralyses.

One of Kemp's (185) experiments at the Central Institute of Agricultural Research, Wageningen, Holland, effectively demonstrates this direct influence of the elements of the *soil* on elements of the *blood*. Eight cows grazed for a year grassland that had received a normal application of potash, while eight others grazed adjacent grassland that had received heavy dressings of potash. It was held that the

TABLE 19

Influence of mineral disequilibrium of grass on the frequency of grass tetany

Ratio $\frac{K}{Ca + Mg}$	Percentage of cattle affected by grass tetany
Under 1.01	0
1.01-1.40	0
1.41-1.80	0.06
1.81-2.20	1.70
2.21-2.60	5.10
2.61-3.00	6.80
3.01-3.40	17.40

N.B. The ratio $\frac{K}{Ca + Mg}$ is expressed in milli-equivalents per kg. of dry matter.

From Kemp (185).

average magnesium content of the blood serum was about 2.4 mg./100 c.c. (considered a normal content in cows), while the magnesium content of the serum of the second group (grazing grass heavily dressed with potash) fell to about 1.4-1.8 mg. This represents a fall of 30-40 per cent of the magnesium content of the blood serum and shows an important disequilibrium of the mineral elements of the blood, resulting ultimately in a deficiency of magnesium. The most effective treatment of grass tetany is an intravenous injection of magnesium salt to the affected animal. This has results as spectacular as those of calcium in milk fever.

It is not a case of abandoning the application of potassium fertilisers, but of apportioning the dressings wisely

It is not for one moment being suggested that the use of mineral fertilisers should be abandoned. What is essential is that their Use is judicious.

A cousin of mine, in 1957, applied 1340 lb./acre [1500 kg./ha.] potassic slag (with 14 per cent potash) in one dressing and managed to

produce two cases of grass tetany in an area where this disease is practically unknown. His daring example is obviously not to be followed.

I recently observed a very informative case in Upper Bavaria. In this mountainous region, where the permanent pastures are hardly ever ploughed up, grass tetany is extremely rare. However, with the co-operation of the District Veterinary Director, I was able to visit a farmer, one of whose cows had been attacked by tetany that very morning.

The farmer and the veterinary surgeon, who was also present, were firm in their assurances that this was the *first* case of grass tetany on that farm. It was pointed out to them that, if this was the case, some change must have been introduced into the grassland-management policy. The pastures had never been ploughed up, and so the question of fertilisers was examined. It appeared that, *for the first time*, the farmer had used a complete fertiliser with potash on his pasture. The quantity applied (29 lb./acre [32 kg./ha.] K_2O), however, did not seem sufficient to start tetany. After further questioning I learned that heavy applications of liquid manure (which is particularly rich in potash) were also made each year at the *beginning* of March. The dressing of potassium fertiliser had been applied at the *end* of March, which meant that the grass had the potash of the liquid manure and that of the mineral fertiliser *simultaneously* at its disposal. The result was immediate "luxury consumption", giving rise to tetany in the animal.

The only advice that I could give to the farmer was to apply his potassium mineral fertiliser *later* in the season, in June, for example, to give the potash in the liquid manure time to be consumed by the grass. This would avoid excessive potash enrichment of the herbage while allowing him to benefit from the increases in yield that stem from the application of potassium fertilisers.

Enormous number of cases of grass tetany on certain English farms

Four years ago I visited an English farm. Previously the farmer had explained to me his methods of management—no permanent pasture and only young leys regularly reseeded, pasture rationed with a single wire, grazing of herbage *always very young*, consideration of rest period completely ignored, enormous applications of fertilisers, and particularly of potash and nitrogen.

This English farmer explained his anxiety, which is that of many other English farmers using the same methods, the frequency of grass tetany on his farm.

It was the month of July, and in a herd of 150 cattle he had had since the beginning of the year twenty-one cases of grass tetany, of which two were fatal.

By mere chance, during lunch, an animal was affected by grass tetany. The wife of the farmer herself made the intravenous injection of magnesium. The animal returned almost, but not quite, to normal. As a result, the vet. was called.

Heal the soil so as not to have to heal the animal

When the vet. had finished his visit we had the opportunity for a chat. I asked him what was, in his opinion, the cause of these many cases of grass tetany on his client's farms. He replied that he did not know. I then put to him the question: "Do you know to what extent your client employs potash on his grassland?" The reply has remained fixed in my memory: "This question concerns the farmer. My role is to care for sick animals and to cure them."

I think that it is exactly this idea which should not dominate veterinary and medical science in the future. It is not merely a question of healing the animal or Man stricken by disease, it is necessary to heal the soil so as not to have to heal the animal or Man.

We concentrate our efforts on the *results* and neglect the *causes*.

Intravenous injection of magnesium salt is good, but if it is the excess of potash fertilisers which causes grass tetany (there may be many other causes) I prefer to reduce or space out these fertiliser applications. It is more economic, and above all it safeguards the health of the animals more certainly.

In examining (in the following chapters) the possible (if not probable) role of magnesium in the two most serious diseases of civilisation, we will better grasp the imperative necessity of concentrating on the *causes* and not on the *consequences*.

The ratio of potassium to magnesium is unbalanced in white bread

Although the subject of this book is not the study of nutritional questions in themselves, but solely in their relationship to the soil, a fact to which I have never seen attention drawn should, I feel, be emphasised: the potassium/magnesium ration in white flour is more than double that existing in wholemeal flour (Table 20, p. 53).

Grass tetany has clearly revealed the serious disadvantages of such an increase, and in the following chapters the consequences with regard to cancer and thrombosis will be examined.

TABLE 20

Mineral elements in wholemeal flour and in white flour

% extraction of the flour	Potassium (K)	Magnesium (Mg)	K/Mg	Calcium	$\frac{K}{Ca + Mg}$	Iron	Copper	Zinc
100	361	106.0	3.41	35.5	2.55	3.05	0.65	3.16
85	179	35.0	5.12	24.5	3.01	2.22	0.36	1.77
80	151	24.0	6.30	21.5	3.32	1.65	0.27	1.30
75	118	16.8	7.03	19.2	3.28	1.35	0.22	1.02
70	111	13.9	8.00	18.9	3.29	1.30	0.22	0.97

N.B. (1) Contents are expressed in mg./100 g. of flour supposed to contain 15 per cent moisture.

(2) The K/Mg and $\frac{K}{Ca + Mg}$ ratios have been calculated by the author but are not given in Horder's book.

From Horder (170, p. 53).

Mention should also be made of the fact that in those countries where supplementation of white flour with certain vitamins and mineral elements is obligatory (170, pp. 159-164) the only mineral element involved is iron, due to the fear that scarcity of iron in white flour is a cause of anaemia (see p. 115). The addition of calcium is optional, and in no case is there any recommendation or obligation to add any of the other mineral elements, magnesium in particular.

Low magnesium content in the blood causes convulsions in humans

This comparison of grass and bread acquires its full significance in the light of a recent observation.

Flink (119), in 1956, in Minneapolis, U.S.A., confirmed convulsions and muscle twitching in patients with a low blood magnesium content.(*). The parallelism between the causes of grass tetany in cows and those of this type of convulsions in Man is truly striking.

(*) It is still not possible to state the *normal* magnesium content of the blood. The figure depends very much, among other things, on the method of analysis. If the method of molybdovanadate titration is used, the normal content would be 1.91 milli-equivalents/litre. If the titanium yellow method is used, the normal figure would be 2.27 milli-equivalents (119). This is further evidence of the limitations of chemical analysis.

CHAPTER 12

*From grass tetany to cancer and thrombosis***Possible lessons to be learned from grass tetany**

GRASS tetany is one of the results of magnesium deficiency. (*) The consequences which this deficiency, whether direct or indirect, may have with regard to two of the greatest scourges of humanity will be examined in the following pages.

Magnesium and cancer

The question of the relationship between magnesium and cancer is a vast one, and gives rise to heated arguments, which, unfortunately, are not always disinterested in the opinions expressed.

More than thirty years ago the French doctor Delbet pointed out that dietary deficiencies of magnesium appeared to cause cancer; and the use of potassium fertilisers, in so far as these are antagonists of magnesium, apparently favoured its development. After protracted study of the work of Delbet (89-90) and his co-workers (301-302), I must say in all sincerity that, although certain of the observations made are indeed disquieting, I failed to find convincing proof for such conclusions.

However, the Dutch workers Tromp and Diehl (94, 373-376), in 1956, stated that the low magnesium content of certain water,(**)

(*) The word "deficiency" is to be understood not in the absolute but in the relative sense. The "absolute" amount of magnesium present may appear to be sufficient, but an excess of potassium may create a deficiency.

In the interests of simplicity the potassium/magnesium ratio has been singled out, but it must not be forgotten that this equilibrium is dependent on many other equilibria, among them the calcium/magnesium ratio. Many workers (270) have shown that a ration very rich in calcium can prevent the absorption of magnesium. Another important ratio is that of potassium/sodium, which plays a fundamental part in cardiac and vascular diseases. Here again the golden rule of equilibrium holds. Too high a concentration of potassium (249, p. 937) has a paralysing effect on the myocardium; inversely, excess sodium, which creates an indirect deficiency of potassium, causes lesions of the myocardium (345). The fundamental role of potassium in muscular metabolism in general should be borne in mind (19).

(**) See Tromp and Diehl's maps (p. 257) for the geographical distribution of cancer in Holland.

particularly of purified river water (16) (the source of drinking-water in many of the spreading towns of today), seemed to be one cause of the much higher mortality from cancer observed in suburbs and districts where purified water of this nature is drunk (see pp. 247-249).

But, I believe that the outstanding discovery of properdine reveals in a new light the action of magnesium in cancer.

Properdine is active only in the presence of magnesium

Details will be given later (see pp. 104-106) concerning properdine, which was discovered some four years ago by Pillemer (282-285). Properdine plays a part in the composition of what is known as the "properdine system", thanks to which the human or animal organism possesses a non-specific power of resistance against attacks by infectious (*) agents. Essential to the functioning of this system are the magnesium ions, *without whose presence it is completely inactive*.

In 1957 the most daring experiment ever undertaken in inoculating humans with cancer revealed the role of the "properdine system" in protecting Man against this dread disease.

Convicts, the guinea pigs of cancer

Southam, Moore and Rhoads (343, 344) of the Sloan Kettering Cancer Institute (New York, U.S.A.) asked the Columbus Penitentiary for volunteers for grafting with cancerous human cells.(**) The aim of the experiment was to compare the development of these grafted cancerous cells: (a) in normal subjects, and (b) in subjects suffering from cancerous tumours. In this way it was hoped to study, and perhaps to determine, factors contributing to the prevention of the development of grafted cancerous cells in certain subjects.

The following facts were established:

Grafted cancerous cells develop much more quickly and much more obviously in sufferers from cancerous tumours than in normal subjects. In two of the former group the development of the grafted cells was unlimited and continuous throughout the whole period of survival (six to nine weeks): in one of these cases the grafted cells gave rise to metastasis in the local lymph glands.

By contrast, in the healthy subjects not suffering from cancerous

(*) Or pathogenic, i.e., capable of causing disease.

(**) This involved homografts of cancerous human cells achieved by means of subcutaneous implantation.

tumours the grafted cancerous cells retrogressed and then disappeared.

The blood of a tumour sufferer is low in the "properdine system"

What was the element that gave the healthy subject such a power of resistance that the cancerous cells were unable to develop, and even were destroyed? Up till now (*) only one element has been found, but it is of tremendous importance.

The subjects who most successfully resisted attack by the grafted cancerous cells were those *whose blood was richest in the "properdine system"*. Conversely, the lowest contents of "properdine system" were found in the blood of subjects in whom the development of the graft had been so rapid that they died within six to nine weeks.

Low magnesium content of the blood favours cancer

It is possible that a low content of "properdine system" in the blood was due to an insufficiency of properdine (**) itself.

But one thing is certain: whatever the quantity of properdine, its activity and efficacy are governed by the amount of magnesium ions present. (***) In other words, a direct or indirect (****) deficiency of magnesium will reduce the activity of the properdine system, that is to say, its content in the blood serum. It might even be said in broader terms that with any disturbance in magnesium metabolism there is the risk of a reduction in the activity of the "properdine system", an element of protection and defence against cancerous cells.

These are hypotheses, it is true, but in view of the fundamental and essential part played by magnesium (****) in the functioning of properdine, they merit all our attention.

(*) With the techniques known at present it has been impossible to establish the formation of antibodies against grafted cells.

(**) Or of complement (see p. 93).

(***) It is not a case of an absolute, but of a relative abundance, i.e., the equilibrium of magnesium in the face of its antagonists, such as potassium.

(****) Hyperthyroidism is always accompanied by a fall in the magnesium content of the blood (119).

(*****) The golden rule of equilibrium applies to magnesium as to every other factor: too much or too little is harmful. Excess of magnesium in the muscles can give rise to serious trouble. Moreover, at the University of Dublin in 1957 Hingerty (159) and Conway found a certain parallelism between the effects of an excess of magnesium ions and an adrenal deficiency.

Thrombosis

Present-day statistics in all countries reveal a higher incidence of thrombosis, with greater frequency of embolism, despite the ever-increasing use of so-called anti-coagulants.

The causes of thrombosis are still partly obscure, but it is known that destruction of the thrombocytes (*) plays a decisive part in intravascular thrombosis. To try to protect the thrombocytes against such destruction is therefore logical.

Magnesium hinders destruction of the thrombocytes

It has been successfully shown *in vitro* (in the laboratory) that the magnesium of the plasma stabilises thrombocytes.

Voelkel (383) was able to confirm this finding in humans by means of parenteral or oral administration of magnesium, whereupon clear stabilisation of the thrombocytes was ascertained. It has been concluded, therefore, that the magnesium of the blood serum is to be regarded as a "physiological antithrombotic" (physiologisches Anti-thrombotikum).

Preventive treatment of thrombosis by means of magnesium

In 1957 Schnitzler (316), at the Gynaecological Clinic, Karlsruhe (Germany), used magnesium (**) to prevent thrombosis in women following childbirth. On the basis of eighteen months of experience he estimated that preventive treatment by means of magnesium was superior to the use of anticoagulants, and accompanied by much less risk.

Spectacular cure of thrombosis using magnesium

At the Johannesburg Institute of Medical Research in 1956 some South African doctors (40) found that parenteral injections of magnesium sulphate produced a "dramatic clinical improvement" in patients actually suffering from an attack of coronary thrombosis or who had previously been the victims of such an attack. Continuing their studies in 1957 they observed that a low magnesium content was *always* accompanied by a high cholesterol content in the blood

(*) Thrombocytes or platelets are small disc-shaped elements in the blood.

(**) Magnesium citrate: administration either oral, intravenous or intramuscular.

serum. To better understand the importance of this inverse relationship, it should be remembered that the cholesterol of the blood serum is generally admitted to play a fundamental role in arterial diseases (142).

Disequilibrium of the mineral elements in the soil and the diseases of civilisation

This survey of the importance of a deficiency (direct or indirect) of magnesium in the diet and of a fall in the magnesium content of the blood serum with regard to the two main diseases afflicting civilisation is all too brief. But the importance of the title of the preceding chapter will now be better understood. It may be developed as follows: "In upsetting the equilibrium of the mineral elements in the *soil*, we upset the equilibrium of the mineral elements in the *blood*." This latter disequilibrium, so far as magnesium is concerned, apparently aids the development of cancer and thrombosis.

Relationship between copper and magnesium in the blood

N.B. This chapter may be omitted by non-specialist readers without prejudicing their comprehension of later chapters.

Disturbance of copper and magnesium metabolism in cancer

REFERENCE will be made later to the many arguments which appear to prove the existence of some copper metabolism disorder in all sufferers from cancerous tumours (see p. 199). The various factors showing the role which a disorder of magnesium metabolism can play in cancer have just been examined. The question may therefore be asked what relationship exists between these two metabolisms—a question which, to my knowledge, (*) has not so far been studied.

The milk-fed veal calf is a deficient animal

A personal experiment may be of interest. The Central Veterinary Laboratory at Weybridge was kind enough to send me Mrs. Ruth Allcroft and to put its laboratory facilities at my disposal for studying various questions concerned with trace elements in my own herd. I should like to take this opportunity of expressing my thanks to the directors and workers of the Laboratory, and to Mrs. Allcroft in particular.

As a secondary experiment we investigated the extent to which milk-fed veal calves (**) are deficient in copper. Milk (see pp. 113 and 118) is very low in copper, so much so, that when one wants to create copper deficiency in *adult* rats or pigs, one feeds them exclusively on milk. It seemed logical therefore to think that the white veal calves, fed *solely* on milk, that find their way into the butcher's shop must become progressively more deficient in copper.

(*) This does not mean that such a study does not exist.

(**) The calves in question are veal calves with white flesh that drink only milk and arrive in the butcher's at the age of six to eight weeks.

In another connection Parr (277), at Weybridge, observed tetany among milk-fed veal calves caused by a deficiency of magnesium: in general, these were relatively old calves.

Parallel fall in copper and magnesium in the blood of milk-fed veal calves

Mrs. Allcroft, my own veterinary surgeon, Dr. Lecomte, and I decided to see whether the copper and magnesium contents of the blood serum fell progressively as the age of the calves increased. It was obviously impossible to ask Mrs. Allcroft to come to my farm every two or three weeks to follow the development of a particular calf. It was decided therefore to take measurements from four milk-fed veal calves that I was in process of fattening: the results are contained in Table 21, below.

TABLE 21

Parallel and progressive fall in the copper and magnesium contents of the blood and blood serum of the milk-fed veal calf

Age of calf (in days)	Mg. in 100 c.c. blood serum		Mg. in 100 c.c. blood	Relative variations in the content of	
	Calcium	Magnesium	Copper	Magnesium	Copper
20	11.0	2.0	0.11	100	100
38	11.0	1.9	0.12	95	109
54	11.4	1.9	0.09	95	91
92	12.5	1.0	0.05	50	46

N.B. (1) The measurements were made on four different calves in the Voisin herd.

(2) The 92-day-old calf went for slaughter the following day.

(3) The blood samples were taken by Dr. Lecomte.

(4) The measurements were made by Mrs. Ruth Allcroft of the Central Veterinary Laboratory, Weybridge (England).

It is indeed remarkable that, although these figures were not obtained from one calf, the copper and magnesium diminish in the same proportion. This parallelism is striking and merits clarification in the future.

CHAPTER 14

The œstrogens of grass

The cultivation of subterranean clover in Western Australia

A GREAT part of Western Australia has succeeded in maintaining 2½ million sheep thanks to the introduction of subterranean clover, of which—almost exclusively—a local early flowering variety is used, namely, *Trifolium Subterraneum*, Var. *Dwalganup*.

Pastures which previously could carry only 0.50 sheep to the acre could carry 1.0-2.0 to the acre after the introduction of subterranean clover, which develops perfectly provided that the soil receives regular applications of superphosphate and, in some cases, zinc, a trace element deficient in this region (80, 81).

Losses caused by subterranean clover

Suddenly in 1941 there appeared sterility phenomena in the ewes which grazed this clover. The percentage of lambing fell to even less than 10 per cent in some flocks. This sterility was accompanied by certain anomalies of the reproductive organs, such as inertia and inversion of the uterus. These complications resulted in the death of almost 30 per cent of the ewes, and were accompanied by other curious phenomena.

The udders of the ewes which were *not* pregnant developed and they yielded milk.

The uro-genital organs of the castrated males were affected by different malformations, which sometimes resulted in death.

It is to be remarked in passing that cattle and horses grazing this subterranean clover reproduced normally and did not show any anomaly.

Research on the œstrogens of subterranean clover

It was evident that these phenomena of ewes and sheep recall those which are produced when a pellet of a synthetic oestrogen, such as stilbœstrol, is implanted under the skin of the animal. The Australian

veterinarians and biochemists applied themselves to research on oestrogens (female hormones) in the subterranean clover.

The work of identification was rendered difficult by the fact that the oestrogen discovered up to then in plants were of the steroid family. Many chemical techniques had to be modified in the course of the research.

Analyses of green grass are only analyses of dried grass

It was made clear in a striking manner that analyses of so-called green grass are only analyses of grass dried more or less rapidly at temperatures more or less high. It was shown that this drying destroyed the oestrogen (36, 37).

It was necessary, then, immediately after cutting to immerse the clover in ethyl alcohol (81) or to extract the juice freshly pressed which was treated and sterilised immediately (202).

I quote this analytical detail of the Australian experiments to show a new aspect of the errors which are made in methods of grass analyses. Actually 100 per cent of routine analyses and probably 99 per cent of research analyses are made with dried grass in which the drying operation is performed after a journey of several hours or more. It is inaccurate and unscientific to call such an operation an analysis of green grass.

Now, the oestrogen, as I have just said, are destroyed more or less partially by drying, but many other bodies—known or unknown—disappear with equal rapidity after the herbage is cut. That is true, for example, in the case of the natural antibiotics (385).

The isoflavones as plant oestrogen

Finally, in 1951 the factor responsible for the oestrogenic activity of subterranean clover was successfully isolated. It was a known substance, namely, genistein, which had already been found in the form of glucoside in leaves and flowers of dyers' broom (*Genista Tinctoria*), whence its name (81).

Genistein is the 5:7:4'-trihydroxy-isoflavone. This oestrogen, then, does not belong to the family of steroids, and there have since been discovered several vegetable oestrogen of the family of isoflavones, for example, in red clover: biochanin (288) (5:7-dihydroxy-4'-methoxy-isoflavone) (see formulae in Fig. 8, p. 63).

The casualties disappeared without anyone knowing why

The discoveries were particularly interesting. However, in my opinion their great lesson lies elsewhere.

Returning to the point from which we started—the sheep flocks grazing the subterranean clover—what happened to them during these ten years of research?

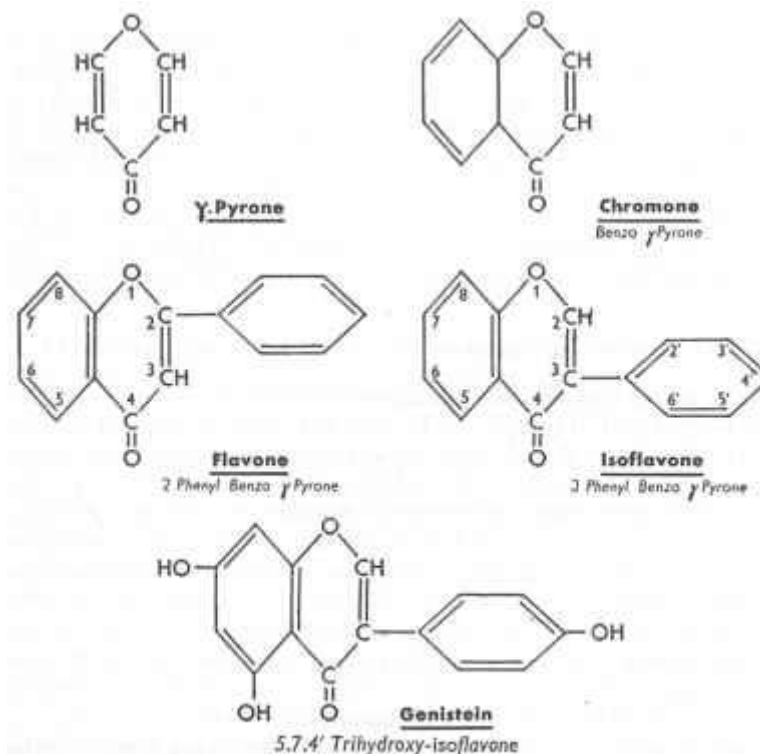


FIG. 8. Formulas for flavone, isoflavone and genistein.

If the Australian farmers had been obliged to wait for the conclusions of their biochemists there would doubtless have been no more sheep in Western Australia.

We come now to the curious fact that from 1943 on casualties became less frequent in the flocks, and they disappeared progressively. I will not detail the devices which the farmers used to modify their grazing methods in order to reduce the percentage of the subterranean

clover, but it was evident that "something else" had intervened to cause the disappearance of the terrible casualties which had been experienced before.

New research towards the end of 1952 (6) revealed the real cause of the increase in the oestrogen content of subterranean clover.

Insufficiency of the application of superphosphates was the cause of the casualties in the sheep

During the first years of World War II Australian farmers were short of superphosphate and could not make the customary applications to their pastures. It was shown that the deficiency in phosphate (and perhaps in sulphur) in the soil leads to a very great increase in the oestrogen content of subterranean clover. From 1943 the supply of superphosphate became more normal, though it was some years later that it became abundant. There lies the explanation of the appearance and disappearance of the casualties. There also lies the real lesson of the disaster which struck the sheep of Western Australia.

Do we employ too much or not enough mineral fertilisers?

Many would make mineral fertilisers responsible for the ills which affect animal and Man and would wish that they should not be employed. We have shown (pp. 35-40) that the cumulative effects resulting from the employment of nitrogenous fertilisers can bring very serious deficiencies, of which the consequences are incalculable. I have, however, been careful to emphasise that it is not a question of prohibiting the use of mineral fertilisers, but of employing them *judiciously*, because many deficiencies which are experienced arise *from the fact that we do not employ enough mineral fertilisers*: in the case mentioned in Chapter 9 we neglected to utilise fertilisers containing copper in order to replace this metal, which our trebled harvest removed from the soil with cumulative effect.

I have in addition cited numerous examples proving that the judicious application of the usual mineral fertilisers improves the quality of the plant and enables the animal to make greater live-weight gains.

The Australian experience has revealed a still more refined aspect of the consequences of *insufficient* applications of mineral fertilisers to the soil. The lack of phosphate (and perhaps of sulphur) in the soil has disturbed a metabolic mechanism in the cells of the subterranean clover, with the result that they are led to manufacture excessive quantities of the oestrogen called genistein.

The conclusion will again be: *excessive* and unbalanced applications

of mineral fertilisers are a danger for the animal and for Man, but *insufficient* applications of these fertilisers are equally dangerous.

Spring grass exercises a stimulating effect on the production of milk

In the course of these observations on the oestrogen of the subterranean clover in Western Australia, attention was drawn to the oestrogen of pastures.

Seasonal variations of the oestrogen content of grass were measured, and it was shown that the high level in spring was probably the cause of the high production of milk of cows grazing spring grass. On the other hand, the very great poverty of the grass at certain times of the year could partially explain the low capacity for milk production of this grass.

Here again is the *golden rule of the mean and the danger of too much or too little in the case of the oestrogen* contained in the pasture.

It also seems that almost always forage and herbage plants lack oestrogen and that it is necessary to raise the content if one wishes to stimulate milk production. A more exact method of estimating the importance and kind of oestrogen in different plants is now required.

Oestrogen content of grass and of various plants

In the last five years research on the oestrogen of grass has been multiplied. Results are shown in Table 22, prepared in 1956 by German veterinarians (317, 318, 319).

I would emphasise only the following point: the enormous richness in oestrogen of the flowers (800 ME) and above all of the stems of the flowers (1788 ME) of the dandelion (ME = mouse-unit per kg. artificial unit).

Here is a remarkable fact: during the great frosts of the winter 1955/56 the pastures of the North-West of Europe had been invaded by the dandelion.

It is the same in my pastures. I have found that each time I put cows into a new paddock they eagerly consume the dandelions and are particularly attracted by the stems of the flowers. The question arises whether the cow, with its extraordinary instinct, seeks, in the dandelion, oestrogen favourable to its health and milk production.

I have said in my book *Grass Productivity* (388, pp. 109, 116) what an extraordinary gourmet the cow is. English experiments (where they had no dandelion) show that the preference of the cows is for

plantain (ribwort), which we know today to be one of the plants richest in natural antibiotics (385).

It is unfortunate that these valuable plants are considered as

TABLE 22

Oestrogen content of various plants

	ME per kg. of dry matter
(1) Grasses:	
Meadow Fescue	1200
Smooth-stalked meadow grass	500
Yellow grass	3400
White Agrostis	1250
Timothy	700
Cocksfoot	1000
Rye-grass—	
L strain	700
O strain	7000
NFG strain	5600
(2) Different Plants:	
Dandelion—	
Before flowering	77
Flowers	800
Stems of flowers	1788
White Clover	83
Red Clover	2270
(3) Mixtures of Plants:	
Grass from pasture (G)	5898
Grass from pasture (W)	922

ME = artificial unit = Mäuseeinheit = mouse-unit.

From Schoop and Klette (318).

"weeds" and farmers are advised to sow "simple" mixtures not containing these so-called "weeds" which are not found to have such remarkable qualities.

Sterility due to liquid manure

Traditional peasant experience is against the application of liquid manure to pastures. It is often stated that this idea comes from the fact that cows do not readily eat grass on which liquid manure has been spread. This is true, but is only one of the reasons which has led farmers all over the world, especially in mountainous districts, to

spread, for preference, their liquid manures on meadows and not on pastures.

It is, in fact, possible to graze animals on pastures which have received liquid manure, after a sufficient interval when rain will have soaked the liquid manure into the soil. Cows then eat this grass very well, but it has been found that they are affected with sterility for some months (317) (temporary sterility).

Veterinarians who have observed this fact have discovered that grass sprinkled with liquid manure has much too high a content of oestrogen, which they attribute to the influence of the hormones contained in the liquid manure.

These studies are insufficiently complete for definite conclusions to be drawn. In view of the current tendency to spread liquid manure on pastures, it is advisable to bear in mind the risks (not mentioning the risk of grass tetany).

CHAPTER 15

The fertility of the animal is a function of the fertility of the soil

Manganese deficiency and sterility in rats and pigs

IT has been observed for some fifteen years that rations with insufficient manganese cause sterility in rats (49, 338) and pigs (178).

It is much more difficult to provide ruminants with rations deficient in manganese because of the considerable weight of these rations, but the problem has been approached in another manner in the state of Wisconsin (U.S.A.).

Sterility in many herds of cows in Wisconsin

For a number of years there have existed in Wisconsin numerous herds suffering from sterility which affected the males as well as the females, but was obviously more apparent in the cows. It was a persistent sterility recurring from one year to another on the same farms.

Studies made in the University of Wisconsin (38) showed that this sterility appeared in the districts where the total manganese content of the fodder was particularly low, namely, less than 20 mg. of manganese per kg. of dry matter, while it is generally in excess of 50 mg. (*) in districts where the fertility of the cows is normal.

Characteristics of the organs of the cow on soils poor in manganese

The manganese content of different organs of the cows were studied in the normal districts and in the districts where the soil was lacking in manganese and causing sterility.

Although the fodders poor in manganese brought about abnormal changes in the structure of the livers of the animals, no difference in

(*) With the reservation that the *total* content does not take into account those forms where manganese is found in the plant.

The fertility of the animal is a function of the fertility of the soil 69

the manganese content of this organ was found. The conclusion was drawn that the animals have a particular capacity—in very different conditions—of maintaining constant the manganese content of the liver (which is not the case with copper).

The Wisconsin scientists finally decided that there was only one organ of the cow in which the manganese content was affected by the richness of the ration in this element, namely, the ovary.

In the case of rations in the districts poor in manganese the ovary of the sterile cow contained 0.65 mg., and even less, of manganese per kg. of dry matter, while the ovaries of cows in the normal districts contained 2 mg. of manganese per kg. of dry matter (38).

If this fact were confirmed, it would be of great importance and an analysis in the abattoir of the manganese content of the ovaries of sterile cows would perhaps provide information on the possible role of manganese in the sterility observed in certain regions.

The analysis of the *total* mineral element of an *organ* does not indicate the *available* amount of this element in the *soil*

These observations, from the point of view of chemical analysis, illustrate the change in status of analysis mentioned earlier. Analysis can give us in a precise manner only the *total* quantity of a mineral element, whether it is a question of the soil, of the plant or of an organ.

It is possible that the manganese of the ovary is found under several forms and combinations, not all exercising the same activity.

But if measurement of the total content of manganese in the soil is not strictly significant there is reason to hope to find a marked significance in the *total* content of manganese in an organ, especially if the *total* content in the organ diminishes when physiological abnormalities appear.

Here, then, is a good example of the change in status of chemical analysis which alone can render this analysis useful in the role of the biological test.

Identical calves can vary in fertility

Among the experiments of the University of Wisconsin there is one which seems particularly interesting and rich in information.

Two groups of female calves (14) were raised on well-balanced and identical rations, except that one of these rations was composed of fodder and grains coming from one of the districts *deficient* in

manganese and that the other group received the same foods produced in normal districts.

The two groups developed in an identical manner and their state of health was the same, and they were served at almost the same age. The heifers brought up on rations from the districts poor in manganese calved before time or produced dead or very weak calves, while those on rations suitable from the point of view of manganese, calved normally, giving healthy calves.

The same experiment was made with male calves. They developed quite normally and uniformly in the two groups, but at the adult age the bulls, raised on the ration poor in manganese, gave a sperm of very low quality. These bulls seldom made cows pregnant. The bulls of the other group reproduced perfectly.

In both cases the troubles disappeared when the ration of fodder and grains of the soils poor in manganese was replaced by those coming from normal soils.

Animals which appear well may be in a condition of latent ill-health

The above experience of the University of Wisconsin is a very good illustration of what at sight appears a paradox and is yet a truth—animals which appear well may be in a condition of latent ill-health.

The male or female calves raised with the fodders and grains coming from soils deficient in manganese have had exactly the *same* development and the *same* appearance as the calves fed on the same ration coming from normal soils. These calves have therefore an identical "biography" and an identical appearance.

No stock farmer or veterinarian would have thought that the calves were developing a fault in their functions of reproduction.

Here, then, is a typical example of the "subtle" influence of a soil element on the metabolism of the reproductive cells only while the metabolism of all the other cells remains intact.

This disturbance of the metabolism of the reproductive cells while all other cells function normally will not manifest itself by any external sign so long as the demands of reproduction are not made on the animal. Here were apparently healthy animals with disease symptoms unrecognised.

If the male calves had been castrated and then fattened as steers the defect would never have been discovered.

Soil of mediocre fertility results in an animal of mediocre fertility

It is logical that a deficiency in the soil insufficient to disturb the metabolism of all the cells of the animal can, however, affect the more delicate mechanism of the reproductive cells.

An American scientist reminds us (2) :

"The greatest physiological burden that a cow endures is that of reproduction. The first injurious action resulting from soil deficiencies will make itself felt in the processes of reproduction of the cow."

I would state further that: "A mediocre fertility of the *soil* manifests itself before everything else by a mediocre fertility of the *cow*."

CHAPTER 16

*Agronomic original sin***Diet of the mother and malformation of the child**

DEAN JOHN B. SAUNDERS of the Californian School of Medicine recently emphasised that the absence of certain elements from the diet of the mother during pregnancy was the cause of many malformations occurring in children. He added:

"Almost all the malformations observed in Man have been reproduced in laboratory experiments with rats by altering the mother's diet during pregnancy. A diet deficient in folic acid (*) produced virtually all known types of abnormality in the hearts, arteries and veins of baby rats.

"There is almost universal failure to appreciate that most defects and malformations in children are not mutations resulting from damage to the genes which do determine potential growth of facial and other dimensions of the child's physical appearance. However, even this control is only potential, and the potentiality may fail to express itself due to *nutritional*, endocrine, toxic and other disorders.

"Billions of dollars are being poured into funds purporting to research the possibilities of alleviating an ever-growing list of conditions which might never have existed, had good nutrition been the national heritage."

Cell metabolism in the child may suffer irreparable damage

The feeding of the mother therefore leaves a permanent physical mark on the child, in the same way as, in the opinion of the Church, Original Sin leaves its permanent moral mark. This particular Original Sin I have chosen to call "*agronomic original sin*" to emphasise its origin. It is an "agronomic influence" to which the mother has been subjected while she bore her child, and which marks the child *forever* through the creation of defective metabolism of certain of its cells. That is the subject matter of this chapter. This influence can equally be exercised through the intermediary of the milk which the newborn drinks, a subject which I will treat in Chapter 18.

(*) Also called pteroyl glutamic acid or vitamin B₉. Occurs in abundance in green leaves, liver and yeast. Valuable in the control of anæmia.

Enzootic ataxia

There exist numerous regions of the world where lambs are affected with a nervous disease which causes a lack of co-ordination in the movements of the animals (34, 35, 36).

The names given to this disease are numerous—sway-back, swing-back, gingin rickets, lamkruis, renguera, etc., etc. I think the most appropriate is **enzootic ataxia**, and I shall use that name here.

The disease especially attacks lambs, but it appears sometimes in calves and occasionally in kids. Generally, the symptoms appear immediately after birth. It sometimes happens, however, that the animal is not attacked until the age of two or three weeks.

The animals remain lying down, moving their heads and making spasmodic efforts to rise in order to suck their mothers. When they succeed, it is only to fall back on their sides. Generally, they can raise only the anterior part of their bodies, the hind limbs being too weak. Those which can move around have badly co-ordinated movements, trying to balance themselves in movement and finally falling.

Destruction of the myelin

Enzootic ataxia is characterised by a demyelination, that is to say, by destruction of the myelin.(*).

The demyelination of the central nervous system demonstrated in enzootic ataxia develops symmetrically. It can appear only as little nuclei in the white mass of the brain or may develop so as to extend completely over the two cerebral hemispheres. In the latter case, liquefaction may occur and symmetrical cavitation may be observed filled with liquid or a clear jelly.

There is always produced secondary demyelination of the motor nerves of the spinal marrow, especially of those controlling the posterior limbs.

Demyelination starts in the foetus

It has been shown that the modifications of the myelin begin to occur in the foetus six weeks before birth and that they continue to develop to a greater or lesser extent until birth.

What is certain is that the demyelination begins always in the

(*) Myelin is the soft substance which is contained in the sheath of Schwann of the nerves. It gives a white appearance to the nerves which distinguish them from the cellular structure of the neurons, which are greyish.

Myelin is formed of neutral fats, cholesterol, lecithin and several brain lipids.

foetus. If it is already advanced, the lamb is dead at birth or dies almost immediately afterwards. In less-severe development, the lamb will live some weeks after birth. If it is a question of a very weak demyelination the lamb will live all its life more or less abnormal.

In the case where instead of a lamb it is a question of a human being we may ask if the many forms of nervous diseases which continually develop are not the consequence of a nutritional deficiency in the mother when she is pregnant.

Oral administration of copper to the ewe prevents the ataxia of the lamb

It was quickly observed that enzootic ataxia was not hereditary and was not caused by bacteria, viruses or parasites.

It was found besides that the disease was localised in certain districts and that *ewes transferred to other pastures did not produce lambs suffering from ataxia*. It was therefore concluded that the pastures were deficient, as a consequence of a deficiency of the soil.

Australian biochemists, able specialists in deficiency diseases, set to work and found that one could prevent the disease by administering copper salts orally to the ewes. The same result was found in England (10, 11).

In both countries the results were spectacular and the oral administrations of copper to the ewes resulted in the almost complete disappearance of the disease.

Lesions of the nerve cells of the lamb are irreversible

What is remarkable is the fact that the administration of copper to the lamb was absolutely ineffective, which indicated that the metabolic disturbance of the nerve cells which was produced in the foetus are of an *irreversible* character. There is a question, then, of an "original sin" which will follow the lamb all its life if it succeeds in surviving.

Deficiency of copper in the soil is the cause of enzootic ataxia

In every case it was proved that this deficiency of the grass in copper was caused by the soil because the application of copper to the pasture resulted in the disappearance of ataxia in the lambs. It is once more to be emphasised that it is not a question of grass poor in *total* copper. That was the case in Australia, where the copper con-

tent of the dry matter of the grass was from 2 to 4 parts per million (*) (that is to say, very low); but in Derbyshire (Great Britain) the grass of the pasture causing ataxia is rich in copper and sometimes the content is as high as 22 parts per million. In the latter case it seems that it is molybdenum, which is antagonistic to copper, which indirectly causes a deficiency of copper. I have emphasised already the complexity of this antagonism, which I cannot unfortunately develop further. However, it is certainly a deficiency direct or indirect of copper in the *soil* which causes in the ewe disturbance of the metabolism of the nerve cells of the *foetus*.

The soil, through the mother, has permanently marked the offspring

Here, then, is a typical case of "original sin" due to the influence on the mother, in the course of gestation, of a soil deficiency.

It is known that such deficiencies can be of natural geological origin, but that they can equally be caused by our *agronomic* methods. We have seen, particularly in the case of copper, how, through cumulative effect, nitrogen fertilisers cause a copper deficiency (pp. 35-40).

It can therefore be said that ataxia is indeed an "original sin", which has its origin in the soil, naturally or because of our agronomic methods.

From ataxia to "raide" of lambs

In certain districts in France lambs are affected by "*raide*" (stiffness), which, indeed, would be more properly called "*flasque*" (flabbiness) (64, 65).

It is not a disease of *grassland*, but of *sheep barns*, that is to say, it is caused by winter feeding. It would seem that in this winter food it is wet sugar-beet pulp which is the principal cause.

In "*raide*" brain cavitation has never been proven. One must, however, not forget that in enzootic ataxia resulting from copper deficiency, cavitation does not *always* occur. It is therefore possible that it is a question of copper deficiency due to a real deficiency in the ration of this element or caused indirectly by the pulp. Unfortunately, no studies have been made concerning copper in the tissues, particularly blood and liver, of the lambs affected by "*raide*" or of their mothers.

(*) "Normal" richness is from 10 to 12 parts per million, with the reservation on this total content that copper may be found in available or non-available forms.

Another important point in "*raide*" is that the nerve cells of the lamb are affected not only in the foetus but by the mother's milk as well. It is even considered that the milk of the ewe alone is responsible and if the lamb receives cow's milk it is not affected by "*raide*". This question is controversial, for the results are not always the same. However that may be, it would seem that the milk plays a very important part in "*raide*".

"Pulp milk"

This is not very surprising since we know that "pulp milk" (or silage milk), i.e., the milk of ewes or cows fed on pulp (or silage) has certain deficiencies.

Up to the present, studies have been made only on aspects which manifest themselves by a loss of money, namely the deficiencies of this milk, which makes it impossible to manufacture hard cheeses. I refer to my treatise on *Biochemical Aspects of Silage* (385), where one will see the immense studies which have led to the conclusion—rightly or wrongly—that silage milk does not contain vitamin H' (*para*-aminobenzoic acid).

Unfortunately, as in many other cases, attention is concentrated on questions where important financial interests are concerned, but sufficient attention has hardly been given to the influence of silage milk on the health of calves or babies.

That brings us to examine the form of "agronomic original sin" which can be attributed to milk. At first we shall consider briefly certain disturbing characteristics of the new selections of white clover.

CHAPTER 17

New strains of white clover which cause bloat and affect the thyroid gland

The new strains of white clover which cause bloat

VETERINARIANS are familiar with numerous accidents observed in young reseeded pastures. Among these accidents, one of the most common is bloat.

These cases of bloat are specially due to the new varieties of white clover, of which the three most common are

New Zealand Strain No. 1
Aberystwyth Strain S.100
Ladino

while the good common white clover of our pastures has never caused bloat.

The selection of forage plants does not take account of the animal

The cause of this disaster is that in the Centres of Plant Breeding varieties of fodder plants have been selected without full consideration of the animal. More exactly the feeling has been that sufficient consideration is given to the animal when one analyses the so-called protein, what is called fibre and the different "extractives", etc.

These new varieties of grass have been and are being selected from experiments on tiny squares which are cut with the shears. There is hardly any concern for the methods of practical management in which these new varieties will have to "live". But the most serious matter which has not been—and is not being—considered is the influence of these varieties on the production and health of the animal.

However, it must be said that the new varieties of white clover cause a few other troubles. It has been found necessary to study the question more closely, and recent observations are more than disquieting.

Selected white clover contains at the same time a cyanogenetic glucoside and a hydrolysing enzyme

The new varieties of very productive white clover, with large leaves, were first selected in New Zealand some twenty years ago. The chemical characteristics which distinguish these selected varieties from ordinary varieties were investigated so as to facilitate the selection and to avoid frauds in the seed trade.

It was found that the highly productive varieties were characterised by the simultaneous presence of (75, 239, 240):

- (1) A cyanogenetic glucoside (*) composed of 80 per cent lotaustralin (**) and 20 per cent of linamarin. (***)
- (2) An enzyme, linamarase, which can hydrolyse the cyanogenetic glucoside, liberating hydrocyanic acid.

The New Zealand geneticists considered that these two characters combined permitted the certification of varieties selected for high production.

In fact, ordinary white clover, whether of the Dutch type (Dutch white clover) or of the "common European cultivated type", contains neither glucoside nor enzyme. Only (****) Kentish wild white clover, widely distributed in England, is slightly cyanogenetic.

The New Zealand geneticists were able to show that the presence of cyanogenetic glucoside and of linamarase was under the strict control of hereditary genes (78).

The two characteristics to which we have just referred helped in the selection of highly productive varieties of white clover, since it was noted that the yield of these white clovers is all the higher as their content in cyanogenetic glucoside is greater.

According to the words of a New Zealand research worker in 1956:

"The agronomic merit of the strains is measured by their cyanide content."

It would seem, therefore, that there was every reason to be satisfied with this criterion of selection of white clover.

(*) Glucose ether containing hydrocyanic acid.

(**) The lotaustralin is composed of glucose, hydrocyanic acid and methyl ethyl ketone.

(***) The linamarin is the lower homologue, where the methyl ethyl ketone is replaced by acetone.

(****) We may recall that a New Zealand investigator (79) stated in 1939 that there existed in the West of France a wild white clover strongly cyanogenetic which morphologically resembled New Zealand Strain No. 1.

Can the hydrocyanic acid liberated in the selected varieties of white clover be toxic to the animal?

The question obviously arises as to whether hydrocyanic acid eventually liberated by the linamarase in the course of digestion may be toxic for the animal. At the end of experiments and calculations the conclusion was reached that the hydrocyanic acid was present in quantities too weak to exercise a toxic action on the sheep or even an unfavourable action on its production.

However, it was necessary to accept the evidence that these selected white clovers had a strong tendency to cause "bloat" in the animals.

In 1948 it was observed in England (15, 113) that the juice of these selected white clovers inhibited, *in vitro*, peristaltic contractions of intestines removed from rabbits.

It was found as well that this white clover juice inhibits in the live sheep the movements of the rumen. The question then arose as to whether the agent causing such paralysis might be the hydrocyanic acid liberated from the glucoside (88).

In Wales it was found that a steer grazing S.100 white clover and which showed the first symptoms of bloat had a blood content of 0.1 mg. of hydrocyanic acid per 100 cc, which is almost toxic.

Thiocyanate—goitrogen (*) factor

In 1949 (76) two New Zealand scientists were able to prove that if, in certain cases, the quantities of hydrocyanic acid absorbed by the grazing animal could be raised and cause an increase of the blood content of this acid the latter was rendered innocuous with sufficient rapidity because it was transformed into thiocyanate.

One might therefore be reassured. Unfortunately different scientists had observed that thiocyanate is a goitre-producing factor because it impedes the utilisation of iodine in the blood by the thyroid (21, 22, 27, 53).

It was shown (120) in *guinea pigs* consuming different white clovers that 100 cc. of their blood serum contain 6.4 mg. of thiocyanate (SCN) in the case of *ordinary* white clover against 13.1 mg. in the case of a *selected* variety of white clover, or more than double.

When *sheep* consumed the selected variety of white clover the content of their serum, which was normally 2.32 mg. of thiocyanate per 100 cc, increased to 8.3 mg. or almost four times as much.

(*) Goitrogen: causing goitre.

Goitre-producing effect of selected varieties of white clover

Experiments with guinea pigs and rats showed a clear-cut goitre-producing effect in selected white clovers (120). In the case of guinea pigs it was shown, for example, that with those consuming *ordinary* white clover, their thyroid contained 0.86 $\mu\text{g.}$ of iodine and that this content fell to 0.33 $\mu\text{g.}$ (or almost one-third less) when these animals were fed a *selected* white clover.

Other observations confirmed these findings, and in 1956 the New Zealand scientists (59, 177) concluded that the selected varieties of white clover, containing high proportions of cyanogenetic glucoside, possessed a *marked goitre-producing character*.

For the better understanding of all the serious consequences of this goitre-producing factor in the new varieties of white clover we will see later the influence that the presence of a goitre-producing factor in any forage plant can exercise on the *animal* and then on *Man*, via *milk*.

But before that it seems to me important to emphasise once more the limits of chemical analysis of our plants.

Goitre-producing white clover is particularly rich in iodine

It is very remarkable that the analysis of white clover shows that the *selected* varieties are much richer in iodine than the *ordinary* white clover.

It was found on the average that selected white clover contained *fourteen* times more iodine than *ordinary* white clover (68.4 $\mu\text{g.}$ of iodine per 100 g. of dry matter against 5.0 $\mu\text{g.}$) (120).

According to classical analysis one would have thought that the new varieties of white clover were very favourable to the proper functioning of the thyroid. That, however, became meaningless because this same clover produced in the blood a factor (thiocyanate) which prevented utilisation of this iodine by the thyroid. That was shown by the biological tests with guinea pigs and rats, but which chemical analysis of the clover—especially routine analysis—could not reveal.

We shall now see another aspect of the goitre-producing effect of green forage fed to our cows.

CHAPTER 18

Milk which produces idiots

Goitre-producing effect of marrow stem kale

AT the Central Veterinary Laboratory in Weybridge (England) it was shown (332) that marrow stem kale causes very serious injurious effects on the foetus carried by ewes consuming considerable quantities of this forage plant.

While the number of lambs born alive and normal was 1.25 per ewe in the control group, the number was 0.5 or less than half of that in the group consuming considerable quantities of marrow stem kale.

In the latter case a high percentage of the lambs were born dead and had a thyroid of abnormal size. Exact measurements showed that the thyroid of lambs born in the control group weighed about 2 g., while the thyroid of lambs born dead or weak coming from ewes which had eaten considerable quantities of marrow stem kale was on the average 22 g., or eleven times more. It was found that in the first case 100 g. of fresh thyroid contained about 50 mg. of iodine, while in the case of the lambs of the marrow stem kale group this content was only 6 mg., or eight times less.

It was concluded that the marrow stem kale eaten by the sheep contained a goitre-producing or anti-thyroid factor.

Variability of the goitre-producing factor of marrow stem kale

The experiments are complicated by two facts. It is not certain—as indeed in the case of other crucifers—that the goitre-producing factor has always the same chemical identity. It is probable (223, 224) that it is a thiouracil or derivative (366).

This chemical variability of the goitre-producing factor can even cause it, under the influence of certain external conditions, to lose this character. The result is—as the Weybridge researches have shown—that if marrow stem kale *very often* contains a goitre-producing factor if does *not always* contain it or at the same level.

There are variations according to the soil and the chemical conditions.

The goitre-producing factor is more abundant under conditions of high rainfall

McCarrison observed in India thirty years ago that the goitre-producing factor is absent in cabbage during dry weather, and becomes very abundant during periods of high rainfall (235, 236). It has been observed that the goitre-producing factor is destroyed by cooking.

Ancient peasant wisdom

As one of the Weybridge scientists has recalled (332):

"Shepherds for generations know that it is dangerous to feed pregnant ewes with large quantities of marrow stem kale. On the other hand, they know well that it is an excellent food for fattening."

Traditional experience of shepherds is found in every country. They did not know that marrow stem kale contains an anti-thyroid factor injurious to the foetus carried by the ewe and favourable to the fattening of the animal at the end of its life, but they acted as if they knew because, from father to son, they had observed the consequences of the presence of this factor.

Events as dangerous as the hydrogen bomb

In 1956 in the Western and South-Western zone of the Pacific several atomic and hydrogen bombs exploded with suitable sensation and effects.

Events, almost equally frightening, have passed in another part of the South-West Pacific, in the Island of Tasmania, and yet few people in the world seem to have heard of them.

Development of goitre in Tasmania

An enquiry in Tasmania (67) in 1949 showed that simple goitre was extremely common there. The frequency varied according to age and sex. The highest frequency was found among girls from 15 to 17 years, and reached the enormous figure of 23 per cent.

At the end of these observations, tablets of iodine were administered to all the children, and five years afterwards a new survey was undertaken. The surprising result was that simple goitre had increased in certain regions among boys as well as girls, while it had strongly diminished in others.

In particular, in two districts, in spite of the distribution of tablets of iodine, goitre had considerably *increased*. The conclusion was reached that the food of the children of these districts must contain an anti-thyroid factor.

Goitre in children increases in frequency with quantities of marrow stem kale consumed by cows

As a result of patient research, and guided by the work at Weybridge, the Tasmanian doctors (67) reached the conclusion that this anti-thyroid factor was contained in the milk of the cows of these districts.

These cows consumed during the winter very large quantities of marrow stem kale. It could even be deduced that the percentage of goitre of the children increased sharply and constantly in proportion to the consumption of marrow stem kale by the cows.

The milk of cows fed with marrow stem kale contains an anti-thyroid factor

In face of the gravity of such an observation it was decided to study more closely the anti-thyroid factor in the milk of cows fed on marrow stem kale. Experiments with rats and mice demonstrated the anti-thyroid action of this milk. Students presented themselves as volunteers and, thanks to radioactive iodine, it was proved that the milk of these cows inhibited the absorption of iodine by the thyroid.

In every case—whether it was a question of Man, rats or mice—care was taken that the control groups received milk from cows consuming ordinary grass. It was shown that this milk did *not* exercise any anti-thyroid action.(*)

"Cretinism" caused by milk containing an anti-thyroid factor

Three groups of fundamental observations can be made:

(1) Two common forage plants: the new strains of *white clover* (recommended at present for sowing down new pastures), and marrow stem kale possess an anti-thyroid factor.

(*) Two other observations of the Tasmanian scientists, one a biochemist and the other a veterinarian, were:

(a) the anti-thyroid activity is found localised in the part of the milk serum which is soluble in alcohol;

(b) the thyroid gland of calves born of mothers fed on marrow stem kale showed different abnormalities—diminution of colloid, increase of the height of the cells of the follicle, hyperplastic modifications, etc., etc.

- (2) This anti-thyroid factor passes into the milk of the cow.
- (3) Simple goitre develops in children consuming such milk.

Cretinism is particularly developed in goitre districts, and the disturbance of the metabolism of the thyroid is reflected in mental capacity. It can be said, therefore, that the milk from cows fed on certain fodders has been the cause of slowing down the intelligence of the children who have consumed it.

There lies another and tragic form of "agronomic original sin".

Agronomic original sin is the principal cause of the mental illness of our children

I attribute part of the cause to the hectic nature of modern life, to the privations and shocks of the War, to the results of venereal diseases, which had already markedly developed before 1939, etc. But I remain convinced that what I call agronomic original sin remains the principal cause of this bewildering number of backward children which we know to exist in France (actually 750,000) and other countries.

In face of the colossal sums dispensed for these unfortunate backward children, how much do we apply to the study of the two questions (among so many others) to which I have referred as types of "original sin" causing more or less disturbance of the nervous and cerebral cells: the influence of copper deficiency (direct or indirect) of the mother on the child and the presence of anti-thyroid factors in the milk of cows fed on certain forage plants.

I would like to be proven wrong and that it could be shown that discreet research workers are engaged in studying these problems, but I am very much afraid that my opinion will not be modified, and that I have to remain with the sad conviction that no research funds have been expended on the study of these two possibilities, only too real, of "agronomic original sin".

CHAPTER 19

Zinc metabolism disorders must be remedied if protection is to be given against diabetes

Automatic device for controlling the sugar content of the blood

DIABETES (diabetes mellitus) is characterised by the incapacity of the tissues to oxidise carbohydrates at the normal speed. One of the principal causes of this disorder is the insufficient secretion of insulin by the pancreas. As a result, excessive amounts of sugar are found in the blood (hyperglycaemia) and sugar is present in the urine (glycosuria).

In normal healthy people an increase in the glucose content of the blood has a stimulating effect on the pancreas, which secretes larger quantities of insulin. Here, therefore, is an automatic device allowing regulation of the sugar content of the blood.

Two types of cell in the islets of Langerhans

Insulin is produced in the islets of Langerhans of the pancreas. Separation of the cells A and B (sometimes called alpha and beta) of these islets of Langerhans has been achieved in recent years (114), and it has been shown that they produce two different hormones with antagonistic effects:

- (1) The A cells produce glucagon, (*) the antagonist of insulin (127), which brings about an increase in the sugar of the blood (hyperglycaemic effect).
- (2) The B cells produce insulin, which diminishes the sugar content of the blood (hypoglycaemic effect).

(*) Also called hyperglycaemic-glycogenolytic factor because it accelerates degradation of the glycogen of the muscles. Equally it increases the breakdown of ketones by thin slices of the liver *in vitro* (in the laboratory).

Insufficient production (*) of insulin by the B cells is one of the causes of diabetes.

Both types of cell in the islets of Langerhans contain large amounts of zinc.

Zinc and insulin

The addition of zinc chloride to an insulin solution retards its physiological action and allows the hypoglycaemic effect of the hormone, if it has been injected, to be prolonged.

Pure, amorphous solutions of insulin have been crystallised with radio-active zinc salts, and it was found (70) that the crystals formed contained about 0.31—0.36 per cent zinc.(**)

Under the conditions of the physiological pH, insulin, which is readily soluble, forms with zinc alone (or with zinc and basic proteins) insoluble complexes which, as will be seen, apparently assume an important role in the B cells of the islets of Langerhans.

Close relationship between zinc and insulin in the islets of Langerhans

An increase in the sugar content of the blood leads automatically to increased secretion of insulin by the B cells of the pancreatic islets of Langerhans. The mechanism is unknown by which the B cells are incited by this higher glucose content to react immediately, discharging more insulin in such a way as to lower that content and return it to its normal level.

It is known, however, that from the functional point of view a close relationship exists in the islets of Langerhans between the movements of insulin and the zinc (***) that is present.

(*) Very probably due to a disequilibrium in production between insulin and glucagon. In healthy people the islets of Langerhans contain 20 per cent A cells and 80 per cent B cells. The constancy of this proportion is remarkable, and any modification signifies a disturbance in carbohydrate metabolism. It has been established that the proportion is modified in favour of the A cells in diabetes, causing excessive production of glucagon relative to that of insulin.

(**) This has led to the supposition that zinc is an essential fraction of insulin, a hypothesis which, however, does not appear very probable in view of the fact that the metal can be replaced by nickel, cobalt and cadmium.

Moreover, the amorphous form of insulin, which probably contains no zinc, has a physiological activity equal to that of the form crystallised with zinc.

(***) Detected histochemically.

The amount of zinc present in the islets of Langerhans is a function of feeding

Okamoto (271) observed in the course of experiments in Japan that the amount of zinc present in the islets of Langerhans was a function of animal feeding. When the ration was *very rich* in carbohydrates there was less zinc in the islets than when the animals had fasted or had received a feed rich in lipids and proteins.

By means of prolonged and repeated increases in the glucose content of the blood, Maske succeeded in ridding the islets almost completely of zinc.

Another important observation made is that after a patient has been treated with alloxan (*) or other substances causing diabetes, the islets lose a large part of their physiological capacity for stocking up zinc.

Insulin is deposited in the B cells in the form of an insoluble combination with zinc

All these, and other analogous observations, led Maske (232), of the University of Munich, to conclude in 1955 that a very close relationship exists in the B cells of the islets between zinc content and insulin deposit. (**)

Zinc and insulin, with or without proteins, form an insoluble complex. Under the influence of glucose (or one of the intermediate products in its metabolism) this combination is split, the insulin rendered soluble and subsequently discharged into the blood circuit.

All zinc metabolism disorders interfere with the functioning of insulin

Zinc is therefore the basic element of the automatic device which retains or liberates insulin, thus regulating the sugar content of the blood. Naturally, this mechanism is thrown out of gear by any substance that upsets the metabolism of zinc; this reveals the fundamental role of one of the "dusts" of the soil in diabetes.

(*) Alloxan (mesoxalyl-urea) allows diabetes to be produced experimentally (334), since it destroys B cells selectively without touching A cells (127). Other substances, such as dithizone (diphenylthiocarbazon), have the same effect. It has been established that these substances combine with the zinc of the B cells, which is then excreted in the urine.

(**) Or at least the immediate precursor of insulin.

The normal function of the islets of Langerhans must be restored

I believe that the information to be derived from these observations goes even further. Up till now, the reasoning that has directed the treatment of diabetes has been the following: the B cells of the islets of the pancreas are no longer capable of producing insulin—the missing hormone must therefore be replaced by insulin injections. Such therapy is based on the *effect* and pays no attention to the *cause*. The following logic might equally well be employed: a disturbance in the functioning of the B cells no longer allows them to produce the necessary insulin; is it not possible to repair this "breakdown" and get the B cells of the islets back into working order?

It appears that a very probable cause of the disturbance is a zinc metabolism disorder. It is not unreasonable to think that if the damage to the B cells is not irreversible they may possibly be incited to begin again their insulin production. This would liberate millions of diabetics from the servitude and dangers of daily insulin injections.

Recent work, in 1955, by Okamoto (272) shows that different substances forming certain combinations with zinc are capable of exercising a protective effect against diabetes.

All this leads us to hope that restoration of zinc metabolism to perfect working order will enable the islets of Langerhans to recommence insulin production.

Protective medicine must prevent zinc metabolism disorders, a cause of diabetes

From the point of view of "protective" medicine, the above reasoning must be pursued still farther. Attempts must be made to prevent zinc metabolism disorders and thereby avoid disturbances in the functioning of the islets of Langerhans. This will necessitate considering all the elements in the diet and in the *soil* likely to cause a metabolic disorder of this "dust".

Such a venture would provide real *protection* against diabetes, for then we should be struggling with the causes and not merely palliating the consequences.

CHAPTER 20

Zinc and premature ageing of the tissues of the prostate gland

Ageing of a cell corresponds to the wearing out of an engine

WHAT is ageing or senescence of a cell? The replies to this question are as vague as they are many, and gerontology, the science of the phenomena of senescence, is still unable to provide even an approximate answer.

Though still somewhat vague, the following reply fits the mechanised age in which we live: "The ageing of the cells of an organ corresponds to the oval piston of an engine." An engine wears out either due to a faulty oil supply or because it has been revolving too quickly. Similarly, it may be said that the cells of an organ have aged prematurely because their nourishment has been defective or because they have been abused.

But what is the reason for this premature wearing of certain cells? Is it because the "dusts" that were previously properly assembled have become misplaced in the harmonious construction of the cell, forming a carbon deposit similar to that found on an old engine?

The answer will be provided by an organ which frequently ages prematurely.

The prostate gland is an organ whose cells frequently age too quickly

This is an organ which ages prematurely in Man and may be considered as a sign of the over-rapid wearing out of his cells. Autopsy has confirmed that in 25 per cent of men over sixty years of age the prostate is no longer normal and is in a pre-cancerous state. This means that the metabolism of the cells of the prostate gland in these men is no longer normal (349).

The swollen gland is removed, but no attention is paid to the causes of the swelling

As long as this abnormal metabolism is not expressed in excessive swelling and does not exert too much pressure on the bladder, little attention is paid to the defect. But whenever the swelling becomes painful there is only one solution: remove the prostate gland, an operation neither easy nor without complications.

An enormous amount of research has been directed towards improving this operation and, from a surgical point of view, the results obtained have certainly been remarkable. Investigational work into the causes of the over-rapid ageing of the cells of the prostate gland, however, is almost completely non-existent—another striking example of the ideas held by modern medicine; effort is concentrated on the *consequences*, that is, on the disease itself, but hardly any attention is paid to the *causes*.

It was only in 1956 that some light was thrown on the imperfect metabolism of a mineral element in the prostate gland.

High zinc content of the prostate gland

In 1952 Mawson (234) showed that in the rat the dorsolateral prostate contains more zinc per unit weight than any other tissue. He established also that activity of the secretional functions of the prostate was always associated with a high content of zinc in the tissues of that gland. Moreover, the tissues of a cancerous prostate gland always suffer from zinc impoverishment.

Drop in zinc content in hypertrophied or cancerous prostate glands

At the Winnipeg Hospital (Canada) in 1956, Hoare (162), using more precise methods, studied the evolution of the zinc content of the prostate as a function of its physiological state. Table 23 (p. 91) shows that even mild hypertrophy of the gland is expressed in a 35 per cent reduction in its zinc content. Where a cancerous tumour is present, the zinc content is reduced to one third of the normal.

Ageing of the prostate goes hand in hand with a disorder in the metabolism of zinc

A fundamental fact is thus revealed: hypertrophy, that is, premature ageing of the prostate gland, goes hand in hand with an upset in

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zinc metabolism, the exact nature of which will doubtless be established by future research. For our present purpose, however, this fact shows clearly the part played by a "dust" of the soil in the premature ageing of the prostate cells. The disturbance in zinc

TABLE 23

Zinc content of the prostate gland, normal, hypertrophied and cancerous

State of the prostate	Microgrammes of zinc per gram dry matter of the prostate
Normal (no hypertrophy or disease)	744
Mild hypertrophy	486
Chronic prostatitis (*)	470
Adeno-carcinoma (**)	273

(*) Inflammation of the prostate gland.

(**) Cancerous tumour.

From Hoare (162).

metabolism may have its origin in zinc not being present in the soil in optimum quantity. It may equally be due to the unbalance of zinc and its antagonists, at least two of which, calcium and copper, are known to us.

Faust's dream will always be a dream

The example of the prostate directs our attention towards the question of the ageing of cells. Unfortunately, it appears as if such ageing represents an irreversible decline. Faust's dream will therefore always remain a dream: a "young" cell can never be made from an "old" one. There is always the hope of escaping cancer or thrombosis, but no one can escape senescence of his cells. All that one can hope to do is to retard the process.

Protective medicine must therefore direct its efforts in the main towards preventing the metabolic disorders which bring about this premature and irreparable wearing out of the cells. Ageing of the cells must be limited as far as is possible. In the case of the prostate gland the aim will be to reduce the speed of breakdowns in the metabolism of zinc as much as possible.

CHAPTER 21

Specific immunity

N.B. The non-specialist reader may avoid this chapter without thereby finding himself in difficulty with the subsequent text. In view of the fundamental importance of this question of immunity, however, the chapter has been written in terms sufficiently simple for it to be understood by the average educated person.

Specific defence

THE organism is able to defend itself against the attack of a *particular* infectious agent by means of a *specific* defence mechanism against that agent *only*. When a person is in possession of a defence mechanism of this nature he is said to possess a *specific* immunity against the infectious agent in question. This specific immunity may be present:

- (a) naturally, following a primary attack (visible or otherwise) by the infectious agent; (*)
- (b) as a result of inoculation with a *specific* vaccine of the infectious agent.

For example, a person vaccinated against typhoid fever can defend himself *specifically* against the infectious agent known as *Salmonella Typhosa*, or "germ" of typhoid fever.

Antigens and antibodies

Any substance that stimulates the production of antibodies and (or) reacts with them is called an *antigen*. *Antibodies* are substances existing naturally or induced by the action of an antigen. They react with the specific antigen that created them.

These definitions do *not in any way* specify the nature of antigens and antibodies: they merely state their existence in their relationship

(*) It appears that a specific immunity of this kind can be transmitted to the foetus through the placenta or to the infant through its mother's milk.

to one another. Such vagueness is demonstrative of the almost non-existent state of our knowledge of the *nature* both of these attacking elements and of our *specific* defence.

Reaction mechanisms of antigens with antibodies are unknown

When we say that the antigens of bacteria create antibodies in the animal or human organism we are simply giving utterance to words.(*). But what phenomena lie hidden behind these words antigen and antibody?

What is known is that the specific reaction of antigen and antibody can take place only in the presence of what is described as the complement.

The complement and its enzymatic character

The complement (or alexin) is a substance contained in fresh blood serum which combines with complexes of antibodies and antigens (even in the absence of any visible reaction). Its characteristics are those of an enzyme.

Like antibodies, the complement:

- has the property, in *specific* defence, of destroying certain infectious agents (pathogens);
- reinforces the action of opsonin (**) in *non-specific* defence as represented by the mechanism of phagocytosis. (***)

The four fractions of the complement

The complement has been fractionated into four component elements designated as C_1' , C_2' , C_3' and C_4' . Despite the studies of fifty years, the chemical nature of the complement or of its components is still unknown. All that is known is that C_1' , C_2' and C_4' are proteins, but the nature of C_3' remains a mystery.

(*) I feel that little progress has been made beyond Ehrlich's diagram of toxin receptors (Toxinrezeptoren), which still provides the best explanation of the combination of phenomena described by the term "immunity".

(**) For opsonin see p. 104. It has sometimes been supposed that the complement and opsonin are identical, in view of their thermolability. This, however, does not seem highly probable.

(***) For phagocytosis see p. 103.

Thyroid and complement

Little is known of the influences that can vary the complement content of the blood, and thereby the organism's capacity for anti-microbial defence, to vary. It has been established (248), however, that hyperthyreosis (excessive thyroid activity) increases the activity of the complement. No one will dispute that the soil, through food-stuffs and drinking-water, exerts a profound influence on the functioning of the thyroid (see pp. 109 and 218).

It is possible, therefore, that the future will see a very marked influence by the soil on the complement which plays a very important part in specific as well as in non-specific defence (see p. 105).

CHAPTER 22

The soil, through foodstuffs, can control specific immunity

Diseases in poultry as a result of domestication

THE animals whose environment and genetic characters have been most upset by Man are probably poultry. As a result, they are liable to a magnificent variety of "civilisation" diseases, but this situation has at least the advantage of making it possible to study the influence of feeding on their specific resistance to various bacteria, viruses and parasites.

Vitamin A, defence weapon against certain bacteria

It has been seen (p. 15) that the carotene (provitamin A) content of plants is governed by the mineral elements in the soil. Investigations into poultry diseases have demonstrated the important role of vitamin A in specific resistance, thus revealing, through this particular vitamin, the influence of the *soil* on *specific* immunity.

One of the best-known examples is that of white scour or pulleriosis caused by *Bacterium pullerosum*, against which vitamin A has a markedly anti-infectious effect (216). When a flock of birds infected with pulleriosis was divided into two groups it was found that the development of the disease was greatly reduced in the group receiving a diet rich in vitamin A, as compared with the group deprived of this vitamin (390).

Role of amino-acids in specific resistance against certain parasites

Many poultry infections are caused by worms such as the *Ascarida*? (*Ascaridia galli*). It has been observed that the resistance of chickens to these worms is considerably increased by an abundance in the ration of such amino-acids (*) as lysine and leucine (301).

(*) Elements constituting proteins.

It is a well-known fact that skimmed milk increases the resistance of chickens to parasites, and Hansen (144), in 1953, was able to show that this was due to its content of the amino-acids lysine and tryptophan. (*)

Mineral elements in the soil determine the percentage of the various amino-acids in the nitrogenous fraction of plants (see pp. 7-12). That the phenomena observed in poultry will extend to other species also is a justified assumption. It may be supposed, therefore, that the "dusts" of the soil, in modifying the amino-acid composition of vegetable foodstuffs, affect the specific resistance of the organism to bacteria as well as to parasitic worms.

Corn (wheat) protects poultry and mice against typhus

One of the diseases that ravage breeding flocks of poultry is typhus, caused by a microbe known as *Salmonella Galinarum*. Smith (342), in 1954, established that the percentage of birds attacked was much higher where birds were receiving a so-called normal, balanced ration than where they were being fed a ration consisting of corn grains. At the Rockefeller Institute (New York) in 1956 Schneider (315) confirmed this finding with mice, whose capacity for resisting typhus microbe (*Salmonella Typhimurium*) is greatly increased by feeding with whole corn. Schneider concluded that foodstuffs contain factors "capable of enhancing natural resistance to infection".

White flour does not contain the factor that protects against typhus

What was the factor present in whole corn (**) that conferred on fowls and mice this resistance against infection by *Salmonella*?

Using refined chemical methods (which he has described in detail), Schneider was able to extract from corn grains the factor enabling mice to resist the typhus bacillus. In this way he obtained the anti-typhus substance in a concentration one million times greater than it occurs in corn. He has not, however, succeeded as yet in determining its exact chemical nature.

What is of particular importance is the fact that *this anti-typhus factor is not contained in white flour*, and has been extracted only from the bran, that is, from the part eliminated from white flour in the milling process. This is a serious matter, one among many that should

(*) See Fig. 2, p. 6.

(**) Up to the present Schneider has found this factor only in corn, commercial dried white of egg and malted barley.

attract the attention of all those responsible for white flour throughout the world (see pp. 52, 53).

Methods of cultivation and specific resistance

Those whose interests are directed to the soil believe that the main task for the future must be to study the influence that methods of cultivation may possibly exert on the presence of the factors of specific defence in foodstuffs, and particularly in cereals. It would be very surprising if the "dusts" of the soil do not have on these factors the same effect as on amino-acids and vitamins.

The influence of manganese on specific immunity to Bang's bacillus seems to confirm this belief.

CHAPTER 23

The manganese of the soil and immunity of the cow against Bang's bacillus

Abortions caused by manganese deficiency are not necessarily of an epizootic character

FROM the experiments of the University of Wisconsin, described on pp. 68-71, it was proved that deficiency in soil manganese caused defects in reproductive functions in cattle. These defects often took the form of abortions. One of these scientists, however, emphasised the following point:

"We found numerous abortions in cows fed on fodders and grains produced on soils deficient in manganese, but *no micro-organism of brucellosis* (*) was found in the foetus of the cow, which indicates that these abortions were not due to this epizootic disease" (36).

On the other hand, in cows affected by brucellosis, spectrophotometric analysis of the blood and of the pituitary gland showed reduced concentrations of manganese (as well as of copper and cobalt) (14).

These observations led to the idea that supplements of manganese salts in the ration could play a protective and/or curative role in epizootic abortion (63).

A mineral salt supplement of manganese in the ration has no effect on brucellosis

Research workers of the University of Wisconsin then undertook trials to ascertain the influence of supplements *in the ration* of trace elements, particularly of manganese, on bovine brucellosis (39). They found that the percentage of epizootic abortion was the same

(*) Brucellosis is the name given to two diseases caused by bacteria called brucella?: contagious abortion and Maltese fever: Brucella; of epizootic abortion of cattle is called Bang's bacillus. For brucellae, see p. 155.

in the control group of cows as in those receiving this supplement. It was, therefore, concluded:

"It would seem that there is no justification for the claims which have been made concerning the favourable prophylactic and therapeutic influences exercised by supplements of manganese salts in the ration on bovine brucellosis."

These conclusions are correct and yet other experiments in another American University showed that manganese plays an important role in brucellosis.

Manganese applied to the soil is effective against epizootic abortion

At the University of Missouri two herds of cows were tested (26). All were affected by epizootic abortion, and the production of milk had fallen heavily. During the entire duration of the study tests were made for Bang's bacillus. One group of cows was fed *only* with feed produced on a soil which had received suitable mineral supplements, in particular several trace elements—including manganese. The trials lasted four years.

All the calves, which were born after their parents had received food produced on the supplemented soil, were absolutely free from the Bang's bacillus, although being continually in contact with infected animals. Having arrived at adult age, the females calved without accident. Furthermore, the health of the group receiving this food coming from the supplemented soil had its health restored at the end of a certain time, (*) the percentage of normal calvings increased considerably and production of milk increased.

Brucellosis, as all infectious diseases, is a biological accident

These experiments led Albrecht to conclude (5):

"Brucellosis suggests itself as an illustration of our undue emphasis on symptoms and pathology, while neglecting causes."

and he said earlier (3):

"Brucellosis is not an infectious disease in the strict sense of the word, but in fact is a deficiency disease."

(*) These observations have again been confirmed recently by Albrecht (5). It would be interesting to see them repeated in different conditions, permitting better control.

Personally, I will add to this by claiming, as in a preceding chapter: "Brucellosis, as every infectious disease, is a *biological accident* due to a disturbance of the metabolism of the cells, which has finally deranged the system of defence enzymes."

Having examined this point, let us compare the experiments of Wisconsin and Missouri, and we shall note the appearance of another fundamental fact.

The mineral element does not exercise the same influence when it is applied to the soil as it does when added to the ration

At first sight these results of the University of Missouri appear to contradict those of the University of Wisconsin, and there has been much discussion between the research workers of the two Universities.

In the experiments of the University of Wisconsin it was shown that the addition of supplements of manganese salts to the *ration* exercised no influence on brucellosis. (*)

On the other hand, in the University of Missouri experiments it was shown that the application of manganese salts to the *soil* exercised a profound influence on brucellosis.

The "organisation" by the plant of the mineral element of the soil

This shows that it is not the same thing to apply a trace element to the animal *directly* in the form of a mineral salt or *indirectly* through the intermediary of the plant.

As we have said, this trace element exercises a profound action on the composition of the proteins of the plant; but, besides, using the expression of Albrecht, the trace element of the soil is "*organised*" by the plant. Lady Eve Balfour (26) quotes the words of the American scientist:

"The same fallacy, concerning the role of minerals, he believes, is shown by the mineral supplement practice in compounding animal rations, which is based on the assumption that supplementing the ration with lime or with phosphate brings the same improvement as putting these through the plant. Such reasoning, he says, gives calcium and

(*) Recent laboratory studies have seemed to confirm (109, 133) the non-action of supplements of mineral salts of manganese on bacteria. In fact, in 1958, Gerhardt, of the University of Michigan, has not been able to confirm any clear action of manganese salts on brucellae cultures (bacteria of epizootic abortion, see p. 155). Unfortunately he has not tried "organised" manganese, that is to say organic combinations extracted from grass or any other plant.

phosphorus put into the soil no other function than to be dragged into the plant to occupy space there, to be thus transported into the animal's digestive tract as they would be if shovelled from the rock pile into the ration."

The mineral elements of the soil are in fact transformed by the plant into organic compounds which have a dietetic value very different from the same element under its mineral form.

It does not come to the same thing to add cobalt to the ration as to add vitamin B₁₂

It is well known that it is not the same to give cobalt and vitamin B₁₂ (which contains cobalt) to a pig or to a man.

Today vitamin B₁₂ is manufactured from cobalt by an actinomycete named *Streptomyces Griseus*.

We may say that this micro-plant has "organised" into vitamin B₁₂ the cobalt contained in the nutrient solution.

Returning to grass, we know that there exist in it chelates (*) of copper much more effective than copper sulphate, which, however, as we have seen, is effective when added in this form to the ration.

These experiments of the University of Missouri confirm that a mineral element of the soil contributes, in the cell of the animal, to the creation of defence enzymes capable of resisting bacterial attack.

Another aspect of this conception will be shown later with a virus, and then with another bacterium.

(*) Organic complexes of a metal.

CHAPTER 24

Role of phagocytosis and properdine in non-specific immunity

Non-specific defence against microbial attacks

IT has just been seen that the organism possesses *specific* mechanisms, particularly antibodies, to defend itself against a particular and definite infectious agent. In addition, however, it possesses a defence system *of a general nature*, which comprises wow-specific mechanisms for anti-microbial defence, it being understood that the designation "microbes" includes bacteria as well as viruses, protozoa, etc.

Fever, a non-specific defence reaction

The most familiar mechanism of wow-specific defence is fever. It is more than two thousand years ago since Hippocrates said, "Fever represents the effort of the organism to defend itself against a disease: it purifies the body like a fire." There was probably the same idea behind the declaration of Charles Nicolle, the French Nobel prize-winner, that: "Infectious disease is the reaction of the human, animal or plant organism against evil forces infinitely small in size."

Hoff (164), Director of the Faculty of Medicine in the University of Frankfurt, has made an important contribution to the better understanding of the mechanisms of *non-specific* defence in the organism. He has frequently emphasised that there is too great a tendency to confuse fever and disease: the former is only a *non-specific* defence reaction to the latter.

What are the metabolic mechanisms that accompany fever?

It would be of the utmost interest to know what metabolic mechanisms, be they cause or effect, accompany fever. One might then be capable of withstanding this general reaction of the organism, and perhaps even of putting the defence it offers into effect while avoiding some of the painful consequences of fever.

The Greek philosopher Parmenides said, with confidence: "Give me the power to create fever and I will cure all ills." If he were alive today, his philosophy tinged with biochemistry, Parmenides would probably say: "Give me the power to reproduce the metabolic phenomena that *accompany* fever and I will cure all ills."

In this and in the following chapters some of the mechanisms that accompany fever in wow-specific defence will be examined.

Phagocytosis

From the scientific point of view the non-specific defence mechanism that has been known longest is phagocytosis, in which certain white blood corpuscles (phagocytes) attack and digest foreign particles, particularly bacteria. Among the phagocytes are found polymorphonuclear leucocytes (white corpuscles), also called granulocytes.

It is now fifty years since Metchnikoff drew attention to the role played by phagocytes in the *non-specific* defence of the organism against infectious agents. Nevertheless, practically nothing is known at present (*) of the intracellular, biochemical mechanisms which enable the phagocytes to destroy the foreign particles they have digested. All that is known is that the micro-organisms that have been "ingested" are "digested" in the cytoplasm of the phagocytes.

Catalase activity of leucocytes

This ignorance of the mechanisms of phagocytosis is the more amazing since it was observed as far back as 1931 (175) that leucocytes have a very vigorous catalase activity. (**) This question of catalase in leucocytes, and particularly in phagocytes, has not been much studied since that date.(***) a situation all the more regrettable in

(*) The few studies that have been made of the problem (308) indicate that it is improbable that the micro-organisms are "killed" by the proteolytic enzymes of the phagocytes, since living bacteria flourish in the presence of large numbers of enzymes of this type.

Hirsch (161), who studied this question in 1956, came to the conclusion that the cytoplasm of the polymorphonuclear leucocytes destroyed the micro-organisms absorbed by means of three elements: (1) acids; (2) lysozyme, a protein of low molecular weight, which enzymatically decomposes certain amino-polysaccharides; (3) phagocytin, the nature and mode of action of which has not yet been determined, but which has no relationship with properdine, since it acts in the absence both of the complement and of magnesium ions. Hirsch makes no mention of catalase.

(**) For the definition of catalase and its functions, see pp. 112.

(***) I only know a recent and short study of Frisch-Niggemeyer in Vienna.

view of the fundamental part now known to be played by catalase (see pp. 155-157) in the battle being waged among cells. (*)

Opsonin

Since 1895 it has appeared that phagocytes can implement their defence action efficiently only if the bacteria have been previously "prepared" by the action of a substance contained in blood serum, given the name "opsonin". This substance is an element of *non-specific* defence, but the quantity in which it is present in blood serum is augmented as the result of immunisation with a vaccine.

There is a correlation here, therefore, between non-specific and *specific* defence resulting from immunisation with vaccines. (**)

Properdine and the non-specific, bactericidal character of blood serum

In certain circumstances blood serum deprived of phagocytes is known to have a truly bactericidal capacity. Study of this characteristic of the blood was to lead to the most sensational fact discovered in bacteriology in the course of the past four years.

In 1955 Pillemer, in the U.S.A., discovered in blood serum a protein previously unknown which was closely connected with the serum's capacity for non-specific resistance and with its bactericidal power.

When zymosan (***) is added to blood serum (at a temperature above 10° C.) it forms an insoluble complex with properdine. A serum thus deprived of its properdine loses its bactericidal character, but regains it as soon as the properdine that has been removed is replaced.

Properdine's mode of anti-bacterial defence is different from that of antibodies

It was thought at first that this was a reaction of the antigen-antibody type (pp. 92-93) on the part of the polysaccharides of the

(*) It will be seen (p. 107) that cortisone, a hormone secreted by the adrenal glands, diminishes the capacity of phagocytes to "digest" the "ingested" bacilli.

(**) It was seen above, moreover (p. 93), that the "complement" strengthens the action of opsonin.

(***) Zymosan is a polysaccharide of the cellular membrane of yeast: it is the insoluble residue remaining after fresh yeast has been treated with trypsin and alcohol.

It should be noted that properdine also combines with the polysaccharides of the cellular membranes of bacteria in exactly the same way as with those of yeast.

bacteria, on the one hand, and properdine, on the other. It quickly became apparent, however, that the formation of complex substances by properdine and the substances of the membranes of the bacterial cells was quite different from the antigen-antibody reaction.

In fact:

(1) (a) The antigen-antibody reaction requires the presence of the four component elements of the complement(*) but not that of magnesium ions.

(b) This combination renders inactive elements C_1 , C_2' and C_4' , but *not* element C_3' of the complement.

(2) (a) Properdine can effect its bactericidal action in the presence not only of the four component elements of the complement but also in *the presence of magnesium ions*.

(b) This reaction renders *only* element C_3' of the complement inactive.

These biochemical characteristics thus clearly express the difference between: (a) the reaction of *specific* antibody-antigen defence, and (b) the reaction of *non-specific* defence by properdine with the cellular membranes of the bacteria.

Relations between *specific* and non-specific defence

The complement obviously creates a bond between *specific* (antigen-antibody) and non-specific (properdine) defence. From this it is to be assumed (**) that there is a close relationship between the two types of anti-microbial defence.

It would appear that the two types of defence, at least at the beginning of a bacterial attack, are not simultaneous but develop successively. Properdine assures the immediate and urgent defence of the organism against all bacterial attacks. It is only after a certain period of time that specific antibodies are formed under the stimulating influence of the antigens.

Properdine, a defensive enzyme

Pillemer stated that properdine functions as a defence enzyme, although the nature of the enzyme has not yet been able to be defined. Reference will be made later (pp. 155-157) to the enormous part

(*) See p. 93.

(**) Other phenomena which cannot be dealt with here appear to confirm this. What will be seen is that catalase appears to play a large part in *specific* as well as in non-specific defence.

played by another defence enzyme, catalase, not only in the anti-microbial defence of the organism but also more generally in the battle between living cells, whether it is a case of two bacteria struggling against each other or one bacterium waging war against a cell of the human lung.

Through the medium of magnesium the soil controls the organism's capacity for non-specific resistance

The name "properdine system" is given to the combination constituted by:

- (1) The protein, (*) i.e., the properdine itself.
- (2) The four elements of the complement.
- (3) The magnesium ions.

The magnesium of the properdine system can be replaced neither by sodium nor by calcium (17), with the result that, under present conditions, *magnesium plays a fundamental part in the mechanisms of non-specific defence* of the organism against infectious agents.

It has also been seen (pp. 56) that the properdine system, and in consequence the magnesium ions, appear to assume a fundamental role in the defence of the organism against cancer: grafted cancerous cells developed only in patients whose blood was low in the properdine system. It is known, moreover (p. 47-52), that the magnesium of the blood is *subject to strict control by the "dusts" of the soil*. Thus is revealed, in striking relief, *the role which the soil plays in the non-specific defence of the organism, whether against microbes or against cancer*.

This role will become even more apparent (p. 120-127) in dealing with the importance of copper in *non-specific* defence.

(*) An euglobulin of which human blood serum contains 0.002 per cent, that is, less than 0.03 per cent of total protein in the serum.

CHAPTER 25

Rôle of hormones in non-specific defence

N.B. Non-specialist readers may omit this chapter without thereby incurring difficulty with succeeding chapters.

Stress

THE idea of "stress" is the creation of Selye (330) of the University of Montreal. By it he understands not only the attack suffered by the organism but also the latter's reaction to that attack. The great merit of Selye and his co-workers is that they revealed the importance of the hormones of the pituitary-adrenal system in the complex of wow-specific defence. (*) Their work has helped to show that in addition to acquired *specific* immunity there are many *non-specific* mechanisms capable of modifying the resistance offered by the tissues to pathogenic agents. As Dubos (99) of the Rockefeller Institute so admirably puts it:

"The results of studies undertaken by several research workers operating separately have clearly proved that the susceptibility of animals to a bacterial infection can be modified at will by a certain number of *non-specific*, physiological and biochemical disorders. These observations imply that the relationship between the organism and the pathogenic agent are markedly modified by a certain number of processes *which are independent of those operating in acquired SPECIFIC immunity*."

Some of the hormonal mechanisms that participate in the *non-specific* defence of the organism will now be examined briefly.

Cortisone reduces the ability of the phagocytes to digest the ingested microbes

Emphasis was placed above (p. 103) on the fundamental role of certain blood corpuscles known as phagocytes in the wow-specific defence of the organism: the cytoplasm of these cells "ingests" and then "digests" the microbe.

(*) My idea of *non-specific* defence corresponds with Selye's "adaptation" and Hoff's "*unspezifischer Abwehrvorgang*" (164, p. 37).

The work done by Selye and his co-workers has demonstrated clearly that injections of cortisone (*) reduce the organism's capacity to resist attack by many pathogenic agents. Confirmation of this has been obtained particularly in the case of the tuberculosis bacillus (see p. 150), research carried out at the University of Pennsylvania (215) having shown that in this instance the hormone exercises a general influence on the phagocytes, shock troops in the defence forces of the organism. The extraordinary fact emerged that the phagocytes continued to "ingest" the pathogenic bacillus normally in their cytoplasm but were no longer able to "digest", that is to say, to destroy it.

It has been agreed, therefore, that certain of the enzymatic mechanisms of the phagocytes were thrown out of gear by this cortisone. Unfortunately it is not known whether this is a case of the hormone influencing the catalase, (**) an enzyme which assumes a fundamental role in the struggle between living cells (see p. 155).

This leads to an examination of the relationship between the thyroid and the pituitary-adrenal system, the role of which, as our knowledge of the subject increases, becomes more and more obviously fundamental in the specific and non-specific defence of the organism.

The pituitary and the thyroid are linked by an automatic device

The endocrine glands control and maintain the general metabolic equilibrium. By means of a perfect, automatic mechanism any slight variation in the amount of hormone secreted by one of them sets in motion modifications in the secretion of the antagonistic hormones produced by the others.

The reciprocal relationship between thyroid and pituitary is so well known that mention need only be made here of the fact that the pituitary secretes a hormone known as thyrotropin which stimulates the production of thyroid hormone (or thyroxine) by the thyroid. As the amount of thyroid hormone in the blood *diminishes*, the secretion of thyrotropin by the pituitary *increases*. This automatic device stimulates the activity of the thyroid, which sets about secreting more thyroxine. Conversely, if the thyroxine in the blood

(*) Steroid hormone secreted by the cortex of the adrenal glands. The steroids embrace many substances, such as the sterols, the acids of the bile, certain cardiac poisons, the sex hormones, etc.

(**) It is noteworthy here that *in vitro* observations (160) have shown cortisone to reduce the production of lactic acid by the leucocytes. One may wonder whether lactic acid is not the element, or at least one of the elements, which, in the phagocytes, destroys the ingested bacillus.

increases to any great extent, the production of thyrotropin diminishes.

Direct relations between the thyroid and adrenal glands

The close connection between thyroid and adrenal glands is less well known. (*) This relationship is made clear by recent investigations. For example, the main clinical and histological confirmation is to be found in the fact that absence of the steroids produced by the adrenal cortex brings about hypertrophy of the thyroid (193). Conversely, thyroid secretion directly influences the adrenal glands. As was shown by Jeanne Raynaud (293) of the Pasteur Institute, Paris, in 1957, administration of thyroxine to mice gives rise to intensive cortisone secretion by the adrenal glands.

Negative correlation between secretions of cortico-stimulin and thyrotropin by the pituitary

It has been successfully demonstrated (54) that there is often an *inverse* relationship between amounts of cortico-stimulin (A.C.T.H.) (**) and amounts of thyrotropin (T.S.H.), both of which are liberated into the blood by the pituitary. *Indirectly*, then, a relationship is revealed between the thyroid and adrenal glands, because when the activity of the thyroid is stimulated by *increased* quantities of thyrotropin the adrenal glands become less active due to the *reduced* production of A.C.T.H. by the pituitary.

The soil, through the thyroid, plays a part in "stress"

Mention was made above of Selye's idea of "stress" and of the fundamental role which this Canadian worker attributes to the pituitary-adrenal system in the non-specific defence of the organism against any aggression it may encounter, whether in the form of traumatism or of an infectious agent. The relationship of the thyroid with the pituitary and adrenal glands illustrates clearly the role of the former in the non-specific defence mechanisms of the organism.

Up till now no clear and direct influence of the soil on the pituitary and adrenal glands has been discernible, although it does seem probable that such a relationship exists. What is known, however, is that

(*) The adrenal glands are two glands with endocrine function situated above the kidneys.

(**) Hormone of the pituitary which stimulates the secretion of certain steroids by the adrenal bodies.

the functioning of the thyroid comes *under the strict control of the elements in the soil*. It is certain, therefore, that *the soil*, through the medium of the thyroid, *exerts an influence over the pituitary-adrenal system* which occupies a fundamental position in the organism's mechanism of *non-specific defence* against all external attacks.

CHAPTER 26

*Copper deficiency upsets the synthesis
of catalase*

The two vulnerable fractions of the defence enzyme

BEFORE dealing with catalase, the fundamental *defence enzyme*, attention should be given to the constitution of enzymes and how they are governed by the "dusts" of the soil. In ultra-simple terms it may be said that an enzyme is made up of:

- a protein fraction (apoenzyme);
- a prosthetic group (coenzyme) (which generally includes a mineral element).

The same is true of defence enzymes. If one or other fraction of the enzyme is "broken down", or the binding between the two parts is broken, there is the risk not only of cell metabolism being disrupted, but also the fear that the mechanisms of defence against attacks by microbes and their toxins will not function properly, or even may not function at all.

**The mineral elements in the soil control the two fractions
of the defence enzyme**

The mineral elements in the soil, particularly the trace elements, control the defence enzymes in two ways.

(1) The trace element alters the constitution of the protein of the living cell, that is, the first half of the defence enzyme (as seen above, pp. 7-9 and 14-19).

(2) The trace element intervenes in the synthesis of the prosthetic group, the second half of the defence enzyme. It may even be an integral part of the prosthetic group.

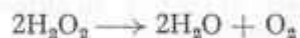
It is understandable, therefore, that a slight variation in the content of a trace element in the soil is sufficient to reduce the capacity of the animal or human *organism* to resist microbial attacks.

The effect which the copper in the soil exercises on catalase, the fundamental *defence enzyme* of living cells, will now be examined in the light of these few general observations.

Catalase

Catalase appears more and more as the enzyme that plays the decisive role wherever two cells are struggling for life. It must be remembered that catalase is an enzyme (ferment) having a protein as apo-enzyme and a heme as prosthetic group. (*) This heme is made up of iron and porphyrin (**) and is similar to, if not identical with, the same radical of haemoglobin.

The function of catalase in the cell is to destroy immediately any hydrogen peroxide (oxygenated water) that may form there:



the formation of this hydrogen peroxide being brought about by certain of the respiratory mechanisms of the cell. If there is a deficiency of catalase, therefore, the hydrogen peroxide is able to exercise its very serious toxic effects on the cell.

Recent research (369), moreover, appears to show that the function of catalase is not solely to destroy immediately the hydrogen peroxide produced in the cell, but that catalase, in dilute solution, thanks to the oxidative coupling, is capable of oxidising a large variety of heavy molecules in the presence of hydrogen peroxide.

Iron deficiency and catalase

Since iron enters into the composition of the heme which forms the co-enzyme of catalase, a deficiency of this metal can reduce the activity of catalase, as was seen above in the case of plants (Table 10, p. 20). There it was a case of a *direct* deficiency due to the absence in the soil of one of the elements involved in the constitution of the molecule. The main concern here, however, is with indirect deficiency resulting from the fact that, as will be seen, *copper is indispensable to the synthesis of the heme*. This phenomenon will also help the reader to understand better the influence of copper in the soil on the defence mechanisms of the cell, in which catalase plays a dominant part.

(*) Or co-enzyme; also called hematin.

(**) Containing four pyrrole rings.

Copper deficiency reduces the activity of catalase in the liver

Schultze (322), in 1941, studied the effect of copper deficiency on various tissues, particularly those of the liver and blood. The deficiency was produced by feeding rats with cow's milk (*) to which a few mineral salts had been added. Table 24 shows the resulting variations in the catalase of the liver of male or female rats (the activity varies with the sex). It will be seen that copper deficiency causes the activity of liver catalase to fall sharply, reducing it to *half the* normal. What is particularly striking is that supplementation of the milk with 0.1 mg. copper per rat per day made the activity increase again very rapidly. This influence of copper was already being felt after *only TWO* days.

TABLE 24

Variations in the catalase content of the liver of rats deficient in copper

	Catalase activity	
	Male	Female
Normal ration	260	143
Ration deficient in copper	102	74
Above ration supplemented with 0.1 mg. copper per day for a period of:		
2 days	123	93
5 days	215	203

N.B. Catalase activity is measured by an artificial mathematical unit.
From Schultze (322).

Catalase in the blood

The catalase of the blood is known to be very active: It is concentrated mainly in the white and red corpuscles. (**) It should be noted that haemoglobin has no catalase activity in itself. (***)

(*) Which is very low in copper.

(**) It has already been noted (p. 103) that leucocytes (white corpuscles) appear to have a catalase activity.

(***) Anaemia is associated with reduced activity of the blood catalase. Conversely, an increase in the haemoglobin content and in the number of red corpuscles very often coincides with increased blood catalase activity. However, catalase activity and haemoglobin (or red corpuscle) content do not always operate together.

Reduced activity of blood catalase in cases of copper deficiency

Schultze (321), in the course of his experiments with rats suffering from copper deficiency as a result of being fed cow's milk, also studied the variation in the catalase activity in the blood. Some of the results he obtained are presented (graphically) in Fig. 9 below. It is evident that a diet deficient in copper progressively diminishes the

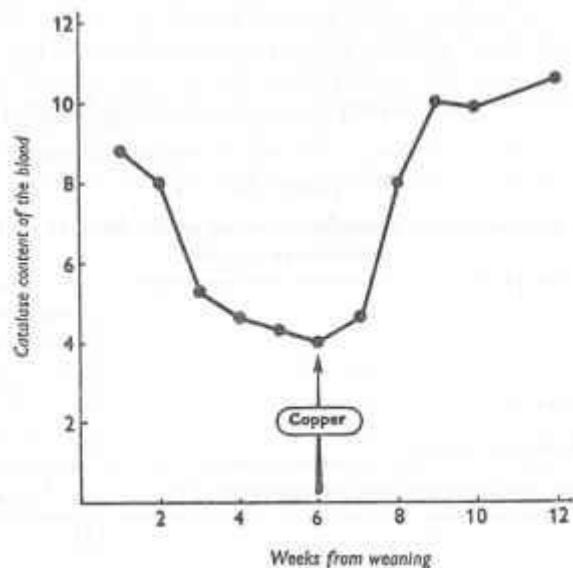


FIG. 9. Influence of copper deficiency on the activity of catalase in the blood of rats.

1. The rats previously fed with a ration deficient in copper were given a supplement of 0.1 mg. of copper per rat per day from the sixth week (indicated by the arrow).

2. Catalase activity is measured in millimolecules of hydrogen peroxide (H_2O_2) decomposed per cubic centimetre of blood in two minutes.

From Schultze (321).

{Drawing by Marthe-Rosine Voisin.}

activity of blood catalase, reducing it to at least half the normal. If the diet is supplemented with copper, blood catalase activity increases, although relatively less rapidly than that of the catalase in the liver under analogous conditions. Nevertheless, less than three weeks after copper supplements were added to the ration, the activity of the catalase in the blood was back to normal.

CHAPTER 27

The organism can utilise iron only in the presence of copper

Copper is essential for synthesis of the heme

As crystallised catalase contains no copper, Schultze was of the opinion that copper deficiency exerts a similar action on:

the activity of catalase in the blood and liver;
the formation of haemoglobin.

Since a heme is synthesised in both instances, the American worker felt justified in concluding that synthesis of the heme is suppressed, or at least very much slowed down, *in the absence of adequate quantities of copper* in the animal organism.

Synthesis of haemoglobin is possible only in the presence of copper

A similar result was obtained some thirty years ago in the case of haemoglobin. As far back as 1928, Waddell (389) and his co-workers showed that if young rats had been rendered anaemic as the result of a milk diet, (*) it was not sufficient merely to add iron salts to the milk. Small amounts of copper salts had to be added *at the same time*, and then the anaemia was rapidly cured (145). These workers concluded that, indirectly, copper is indispensable to the synthesis of haemoglobin.

Anæmia caused by lack of copper is almost identical with that caused by iron

Anaemia caused by lack of *copper* was considered by research workers in general as very similar to, if not identical with, anaemia caused by lack of iron (32, 415). This analogy therefore came to be interpreted as indicating that one single phenomenon was at work in both cases: *a deficiency of iron*, not necessarily due to a lack of iron

(*) Which produces copper deficiency due to the very low copper content of milk.

but to the fact that in the case of copper deficiency *the mechanisms for utilising this iron for synthesis of the hemes are no longer functioning normally.*

Copper is essential if the organism is to be able to utilise iron

These experimental results were largely confirmed from the therapeutic standpoint. In 1957, in Basle, Undritz (378) demonstrated the necessity for copper being present if haemoglobin was to be synthesised and if certain forms of anaemia were to be treated in human beings, or experimentally in animals.

Physiological anaemia (*physiologische Anämie*) in infants and young babies can be reproduced in laboratory animals by creating deficiencies in their diet. Iron treatment may improve the condition of the animals to a certain extent, as has been confirmed in the case of babies. But iron does not have a stimulating effect (*Reizwirkung*) on erythropoiesis: (*) COPPER *must* be administered if normal haemoglobin formation is to take place.(**)

Nothing is known of the mechanism by which copper intervenes in the synthesis of the heme

Despite the agreement evident in all these results, we have still, after thirty years, not the slightest idea of the biochemical mechanism by which copper *governs* the metabolism of iron and, more particularly, the synthesis of the hemes.

In 1956 Underwood, the great Australian specialist in deficiency diseases, concluded (377, pp. 93-94):

"The fact that copper influences iron metabolism, at least in pigs and rats, in such diverse sites as the mucosal cell, the liver and the bone marrow suggests that copper may, in some basic manner, be concerned wherever and whenever iron moves. Knowledge is also lacking of the stage of erythrogenesis at which copper exerts its action. It is apparently not necessary for the synthesis of protoporphyrin. It seems more likely to be concerned with the incorporation of iron into protoporphyrin (***) to form heme."

In other words, in 1956, despite all the work that has been done, no one is capable of telling how copper deficiency impedes synthesis of the heme.

(*) Erythropoiesis is the formation of red corpuscles.

(**) Since cobalt has an equally favourable effect on the formation of haemoglobin in some infectious anaemias, Undritz recommends using a mixture of *organic* combinations of iron, copper and cobalt.

(***) For the porphyrins, see pp. 165, 166.

CHAPTER 28

No attention is paid to the origin of the milk used in experiments

N.B. This chapter may be omitted by the non-specialist reader.

Contradictory results obtained by great scientists

IF all research workers were agreed that copper is indispensable to the synthesis of the hemes, many different opinions were to be expressed regarding the influence of copper deficiency on catalase, particularly the catalase of the liver.

In the course of renewed experiments with pigs the American Wintrobe-Cartwright group (141, 198) had observed no drop in the catalase of the liver. There was a tendency to think that the phenomenon observed by Schultze was peculiar to rats and did not take place in pigs. This reasoning appeared to me to be even less well founded when in 1956 Gallacher (128) failed to observe any reduction in the catalase of the liver of rats deficient in copper. It should be said in all fairness that these authors always had the delicacy not to cast doubts on Schultze's results.

I must admit that I felt somewhat at the mercy of the elements, especially as this work had been done by eminent Nobel Prize-winners. Suddenly, however, in 1957, the Wintrobe-Cartwright group (141) published a paper declaring that copper deficiency in pigs brings about an obvious reduction in catalase activity in the liver. To their credit these scientists openly acknowledged that their present results were at variance with those they had previously obtained. They did not, however, discuss the possible sources of this contradiction.

The origin of the elements used is overlooked

In spite of repeated and attentive reading of the experimental records, no definite statement can be made as to the origin of the

error. I can, however, say that there was one factor which certainly could have caused it. A few words on this matter are of interest because it shows the mistakes that biologists, veterinarians and doctors can make by overlooking (as is almost always the case) the agronomic and pedological (*) origin of the foodstuffs used in their experiments or prescribed for their patients. The matter about to be discussed is, in my opinion at least, of fundamental importance.

What foodstuffs were fed to the cows producing the milk used and what soil produced these foodstuffs ?

It was stated in the preceding chapter that the method generally adopted to create a copper deficiency in animals is to feed them a ration composed almost exclusively of cow's milk.

What milk was used by the Wintrobe-Cartwright group, for example, in their experiments? In the 1952 series (198) *powdered* milk dissolved in water from the town supply (**) was used. In 1957 (141) the basal ration consisted of *evaporated* milk diluted in its own volume of water. *Not a single word is said about the nature of the liquid milk* from which the powdered or evaporated milks were made. What were the cows fed on that produced the milk: grass, beet, silage, etc. ? It should be remembered (see Voisin 385) that milk from cows fed on silage (***) lacks a fundamental element which makes it unsuitable for the manufacture of hard cheeses like Gruyère.

What kind of soil did the grass grow on that provided the food for the cows that produced this milk? It was seen above (p. 46) that the molybdenum (antagonistic to copper) content of milk could vary from one to ten according to the nature of the soil on which the grass had grown.

Is it permissible, therefore, to think that the evaporated milk used in these experiments with pigs will have the same effect on the catalase of the liver whether it contains molybdenum in amounts equal to one or ten?

Variations with age in the biological value of the protein of powdered milk

But even leaving aside the nature of the grass consumed by the cows producing the milk, or the nature of the soil that grew the grass,

(*) Pertaining to the soil.

(**) The nature of this water does not appear to have attracted any attention either.

(***) With the exception of A.I.V. (virtanen) silage. (See page 76.)

there are many other points to examine. Can the influences of powdered and condensed milk on copper deficiency be considered as identical? Were the preparation methods used for these milks always the same?

Mention need only be made in this connection of the work of that outstanding scientist, Kläre Schiller (299, 312, 313) on the variations in the biological value of the casein of powdered milk. After twelve months' storage under normal conditions the biological value of the protein fell from 83 to 51 (313). It may be noted in passing that chemical analysis here again failed to point out any change in the composition of this stored milk powder. Very complicated analyses and a great scientific flair were required to show that, in the course of the ageing process, an essential amino-acid had been inhibited.

Attention must always be paid to the origin of milk used in experiments or prescribed in diets

All these observations serve to illustrate how very different results can be obtained from trials based on a foodstuff so variable, although identical in appearance. It cannot be stated too often, nor sufficiently stressed, that the progress of biological and medical sciences must necessarily be slow so long as no consideration is given, either in experimentation or in dietetics, to the pedological and agronomic origin of the foodstuffs employed.

CHAPTER 29

Increase in the copper content of blood serum in all infectious diseases

Fever is always accompanied by an increase in the copper content of blood serum

IT was stated above (p. 102) that fever is a general defence reaction on the part of the organism and that an effort should be made to understand better the metabolic reactions that accompany it. There might then be some hope of improving the defence potentialities of our cells.

One modification in the composition of blood serum that *always* accompanies fever is an *increase* in the copper content above normal (*) There is, however, another reaction that *almost always* accompanies fever: *diminution* below normal of the iron content. This is shown very clearly by Table 25 (facing) drawn up some twenty years ago by Heilmeyer (153) at the University of Freiburg-in-Breisgau. Unfortunately tables of this nature record only general average contents with which one has to compare the levels of the individual patient suffering from the infectious disease.

A common cold alters the copper content of blood serum

The well-known common cold provides an admirable illustration of the increase that takes place in the copper content of the blood of a patient, mild though the infection may be (Table 26, p. 122).

The work carried out by Wintrobe and Cartwright (411) in 1953 confirmed Heilmeyer's results. Improved analytical techniques and the progress that had been made in knowledge of the forms of copper in blood serum were to allow Markowitz (225) (a member of the Wintrobe-Cartwright group) to go even farther and clear up, in 1955, a very important point.

(*) An increase in the copper content of blood serum is also found in certain physiological conditions (pregnancy) or as the result of haemorrhage.

TABLE 25

*Copper and iron contents of blood serum in acute infectious
diseases*

Sex	Age (years)	Disease	Microgrammes in 100 cc. serum		Notes
			Copper	Iron	
F	41	Scarlet fever: Acute stage 3 days later 6 days later	218 218 210	68 100 146	3rd day of disease, tempera- ture 101.8° F. (38.8° C.)
M	20	Scarlet fever with tonsillitis	163	58	3rd day of disease, tempera- ture 102.9° F. (39.4° C.)
M	25	Diphtheria	251	47	8th day of disease, tempera- ture 100° F. (37.8° C.)
F	27	Typhoid fever	258	41	Temperature 101.1° F. (38.4° C.)
F	30	Simple pneumonia: Acute stage 10 days later	190 126	60 81	Temperature 102.5° F. (39.3° C.) Normal temperature
M	33	Abscess on right lung	239	46	Very serious: died 2 months later
M	34	Abscess on testicles	252	73	Temperature 104.2° F. (40.1° C.)
M	63	Abscess on prostate	215	63	Temperature 104.0° F. (40° C.)
F	28	Endocarditis	263	52	Temperature 102.6° F. (39.2° C.)

N.B. (1) Normal mean copper content is 110-120 µg./100 cc. serum.

(2) Normal mean iron content is 125 µg. in males and 100 µg. in females per 100 cc. serum.

From Heilmeyer (153, pp. 52 and 55).

TABLE 26

Copper content of blood serum in cases of slight colds

Number	Microgrammes copper in 100 cc. serum		Variations (%)
	Before onset of cold	After onset of cold	
1	93	153	+64
2	82	149	+80
3	91	125	+37
4	108	136	+25
5	128	125	-4

From Heilmeyer (153, p. 57).

Caeruloplasmin of blood serum

Earlier, in 1947, the Swedes Holmberg and Laurell (167) had found that in blood serum 90 per cent (and even more) of the copper existed in the form of a combination with a protein. They named the substance caeruloplasmin, because of its blue colour. It seems improbable that this protein may be of use for transporting copper. Moreover, in 1951 the Swedish workers were able to show (168, 169) that this caeruloplasmin fulfilled active functions and that it was a true oxydase.(*)

It has not been possible to determine the physiological role of caeruloplasmin, but this oxydase helps to complete the picture of copper-molybdenum antagonism which was revealed so clearly in the scouring on the "teart" pastures of Somerset (see p. 41). In fact, in 1956 Scaife (309) observed in New Zealand that molybdenum (ammonium molybdate) had an inhibitory effect on the oxydase function of caeruloplasmin.

The caeruloplasmin of blood serum increases during infectious diseases

During different infectious diseases Markowitz (225) carried out parallel measurements of the variations in total copper and caeruloplasmin contents of blood serum, in addition to measuring oxydase activity. Some of the results obtained are contained in Table 27 (p. 123).

(*) Oxydases are enzymes capable of achieving oxidation only in the presence of oxygen.

TABLE 27

Content of copper and caeruloplasmin in blood serum and oxydase activity in the case of infectious diseases

Disease	Micro-grammes copper in 100 cc. serum	Micro-grammes caeruloplasmin in 100 cc. serum	Oxydase activity
Tuberculosis	178	63	8.1
	172	60	8.7
	154	60	7.2
Pneumonia	200	72	7.7
	219	75	9.3
Staphylococcal abscess	219	83	8.0
Sinusitis	203	61	7.6
Mean for these diseases	192	68	8.1
Normal level in healthy patients	110-120	34	3.9

N.B. Oxydase activity is measured with a mathematical unit.

From Markowitz (225).

On the average of the seven cases he examined, the following increases above normal were established:

Total copper	78 per cent
Caeruloplasmin	100 per cent
Oxydase activity	108 per cent

Central position of copper and iron in non-specific, anti-microbial defence

The fundamental role of the two soil "dusts", iron and copper, in non-specific, anti-microbial defence is therefore obvious.

Twenty years ago Heilmeyer was writing (153, p. 115):

"An increase in the copper content of the serum, coupled with a simultaneous reduction in the iron content, is the regular expression of processes of defence against infectious diseases and toxic substances. These variations appear in all clinical and experimental cases of infections or poisoning sufficiently serious to give rise to a defence reaction in the organism. These two metals therefore occupy a fundamental place in the defence processes of the organism."

But how do these two metals intervene in the general defence mechanism of the organism? Heilmeyer's reply (153, p. 115) is as follows:

"It is probable that this defence process consists in impeding the toxins and inhibiting certain of the enzymes of the bacteria simultaneously with catalytic acceleration of cell activity."

An attempt will now be made in the light of recent observations to understand more clearly why these two metals, especially copper, occupy such an important position in *non*-specific defence.

CHAPTER 30

"General mobilisation" of copper in anti-microbial defence

N.B. This chapter may be omitted by the non-specialist reader.

Causes of the higher copper content of blood serum in infectious diseases

IN 1950 Cartwright (62, p. 294) confirmed the higher copper level in blood serum during infectious diseases and underlined the importance of this phenomenon. He concluded: "This phase of copper metabolism is extremely important and deserves intensive study."

Unfortunately the phenomenon has hardly been studied at all, and indeed has been overlooked to a large extent. My two hypotheses will now be advanced in an attempt to explain it.

Does the oxydase activity of caeruloplasmin represent a defence process?

The first hypothesis assumes that this "mobilisation" of forces is going to allow the content of caeruloplasmin to be increased, as was seen above in Table 27 (p. 123). Its oxydase activity would play a part in the general defence mechanisms. This hypothesis, however, would not explain the reduced iron content of the blood serum.

"General mobilisation" of copper is destined to accelerate synthesis of catalase, the defence enzyme against microbes

The tremendous part played by catalase in now-specific anti-microbial defence will be referred to later (p. 155).

This enzyme contains a heme with iron. It contains no copper, but copper is indispensable to the synthesis of the heme (see pp. 111-114). In consequence, I submit the hypothesis that, in the case of infectious diseases, "general mobilisation" of copper must necessarily accelerate

synthesis of the hemes of catalase, a fundamental defence enzyme. This acceleration leads to a greater consumption of iron (used in the construction of hemes) and consequently to the blood being impoverished of that element.

This second hypothesis does not exclude the possibility of the parallel mechanism of the first hypothesis.

The necessity for "general mobilisation" of copper to defend the organism under attack and to accelerate synthesis of the heme of catalase seems to be confirmed by observations made on an analogous mobilisation carried out to speed up synthesis of the heme of haemoglobin.

To accelerate synthesis of the heme copper is mobilised in the blood

Twenty years ago Potter (289) made dogs anaemic by feeding them on a ration deficient in iron and copper, thus considerably lowering the copper content of their serum. Administration of copper *alone* increased the copper content of the serum: a normal finding. But an unsuspected fact emerged: administration of iron *alone* increased the copper content of the blood serum equally rapidly. The American worker concluded from this that the dosing with iron had accelerated the synthesis of the blood corpuscles (erythropoiesis), with the result that copper had been mobilised by the blood which extract it from the tissues where it was stored.

This is in agreement with the observation frequently made that, following a haemorrhage, the copper content of the blood is increased to allow for rapid reconstitution of the red corpuscles lost and thus speed up synthesis of the indispensable hemes.

Copper deficiency reduces the life span of red corpuscles to one-fifth of the normal

Potter's observation was to be confirmed in 1956 by similar findings in Britain and America. In the U.S.A. the Wintrobe-Cartwright group (58) established that in the case of copper deficiency in pigs the average life span of the red corpuscles was reduced from 63 to 13 days (that is, one-fifth) and that the rate of turnover of iron in the red corpuscles was doubled. The Americans concluded that the anaemia that occurs with *copper* deficiency is due both to a shorter life-span of the red corpuscles and to a reduced capacity on the part of the bone marrow to produce these corpuscles.

In the same year in London Gallacher (128) found that in rats

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deficient in copper the rate of synthesis of the heme of haemoglobin is reduced by half.

Synthesis of the heme of catalase is accelerated by copper mobilisation

These various observations show the necessity for "general mobilisation" of copper if quicker synthesis of the heme of haemoglobin is to take place. It seems probable, therefore, that in the case of infectious disease we may find ourselves faced with an analogous mobilisation similarly aimed at speeding up synthesis of the heme of catalase, the fundamental defence enzyme. (*)

Before going on to variations in the copper content of the blood of a patient suffering from a cancerous tumour, it seems expedient to deal with an important point which might give rise to confusion.

Scarcity of copper makes its "general mobilisation" difficult

One must be careful to distinguish between:

- a permanent decline in the copper content of blood serum as the result of a general scarcity of copper; (**) and
- a sudden increase in the copper content of the blood serum as part of the *non*-specific defence against microbial infection.

The question which arouses both interest and anxiety is: what is the result of a scarcity of copper in an animal or human being when attacked by a pathogenic microbe? Will the mechanism for mobilising copper be able to function satisfactorily and efficiently in such a deficient organism?

It seems logical to assume that the "general mobilisation" of copper in the blood will be lower in an organism lacking in copper, whether it is a case of actual impoverishment or of obstructed copper movement (effect of molybdenum and of sulphate). As a result,

(*) It is probable, however, that if it is a matter of one and the same synthesis, two different phenomena are involved. Cartwright (62, p. 293) has in fact found that the increase in copper content of the blood serum in infectious diseases is not accompanied by any observable alteration in erythropoiesis (red-corpuscle formation).

(**) It should be borne in mind that a reduction in the copper content of the blood is not always apparent in cases of copper deficiency (following the combined action of molybdenum and sulphate, for example), but a *permanent*, considerable drop in the copper content of the blood always results from a deficiency.

deficiency of copper (direct or indirect) in the soil will reduce "non-specific immunity" both in animals and in Man.

The importance of this very serious conclusion will become even more apparent on examination of the variations that occur in the copper of the blood serum of a patient suffering from a cancerous tumour.

CHAPTER 31

Increase in the copper content of the Mood of a patient suffering from a cancerous tumour

Defence mechanisms set in motion by the cancerous tumour

HEILMEYER (153) of the University of Freiburg-in-Breisgau put forward the thesis as far back as 1940—and many specialists still agree with him today—that cancerous tumours start up within the organism defence mechanisms analogous to those set in motion by infectious diseases. This point of view seems even more logical today, for it is not now held to be impossible (see pp. 175-177) for a close relationship to exist between cancer and viruses. Moreover, there is no doubt that certain forms of cancer, particularly leukemia, can be transmitted by viruses (or at least by particles that behave like viruses).

The copper content of the blood serum of a cancer sufferer may be trebled

Some of the results published by Heilmeyer in 1941 (153) are contained in Table 28 (p. 130). They seemed to attract little attention until 1952, when Pirrie (286), of the University of Glasgow, published results on which Table 29 (p. 130) is based. Analogous findings appeared from Wintrobe and Cartwright (411) in the U.S.A. in 1953, and in the same year Keiderling (183), a co-worker of Heilmeyer, published results from which the very characteristic and telling graph reproduced in Fig. 10 (p. 131) is extracted.

One fact emerges very plainly from all these observations made by different research workers in different countries, namely, that the amount of copper in the blood serum of every tumour sufferer *increases considerably*, and may even reach three times the normal level. Here, then, is a reaction parallel to that observed with infectious diseases and fever, although the increase is generally more marked in the case of cancer.

So far as iron is concerned, there is an obvious difference between cancer and infectious diseases. While in the latter instance there is

TABLE 28

Copper and iron contents of the blood serum of patients suffering from cancerous tumours

Age	Sex	Cancer of	Microgrammes in 100 cc. serum	
			Copper	Iron
68	M	Bronchi	224	44
53	M	Gall-bladder (with metastasis of liver)	144	131
65	M	Oesophagus	145	—
49	M	Pancreas (with severe jaundice and general metastasis)	237	62
54	F	Stomach (with severe anaemia)	164	41
69	F	Pancreas (with anaemia)	233	—
74	M	Rectum	210	107
53	M	Liver	262	102
51	F	Stomach and anus	213	47

N.B. (1) Normal mean copper content is 110–120 $\mu\text{g.}/100$ cc. serum.

(2) Normal mean iron content is 125 $\mu\text{g.}$ in males and 100 $\mu\text{g.}$ in females per 100 cc. serum.

From Heilmeyer (153, pp. 92–93).

TABLE 29

Contents of iron and copper in the blood of sufferers from cancerous tumours

Age	Sex	Cancerous tumour	Microgrammes in 100 cc. serum	
			Copper	Iron
54	M	Carcinoma of lungs	184	73
61	M	" "	325	40
62	M	" "	211	96
38	M	" "	326	65
39	M	" "	178	57
43	M	" "	211	57
67	M	" "	311	43
35	M	Sarcoma of femur	262	56
69	M	Carcinoma of prostate	174	95
71	M	" "	193	81
58	M	" "	138	105
67	M	Carcinoma of tongue	178	43
71	M	Carcinoma of penis	124	105
59	M	Carcinoma of oesophagus	263	30
67	F	Carcinoma of breast	213	74
58	F	" "	293	40
38	F	" "	245	50

N.B. (1) Normal mean copper content is 110–120 $\mu\text{g.}/100$ cc. serum.

(2) Normal mean iron content is 125 $\mu\text{g.}$ in males and 100 $\mu\text{g.}$ in females per 100 cc. serum.

From Pirrie (286).

almost always a reduction in the iron content of the blood serum, this phenomenon occurs frequently but quite irregularly in the sufferer

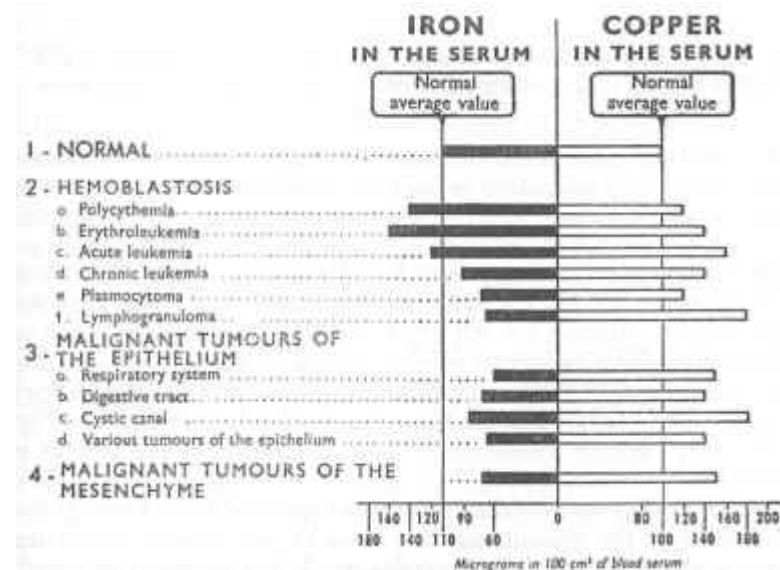


FIG. 10. Iron and copper contents in the blood serum of patients with various cancerous tumours.

From Keiderling (183).

(Drawing by Marthe-Rosine Voisin.)

from a cancerous tumour. There are even a few cases, although these are not common, where the iron content increases above the normal level.

When the cancerous tumour disappears, the copper content of the blood serum returns to normal

When the tumour disappears (surgical removal or destruction by radiation), the copper content of the blood serum tends to diminish and return to normal, where it remains so long as there is no recurrence of the tumour. This form of "reversible variation" in copper content is also observed under the influence of certain "anti-cancer substances".

But except in cases of disappearance (unfortunately often temporary) of the tumour, the increase in the copper content of the blood of

a cancer patient must be looked upon as *semi-permanent*, whereas in the case of infectious diseases this increase was seen to be sudden and of *short duration*.

In the leukemia sufferer increase in the copper content of the blood serum is the expression of the temporary effectiveness of a treatment

An excellent experiment carried out by the American Wintrobe-Cartwright group admirably reveals the parallelism existing between the gravity of a tumour and the copper content of the blood serum. In 1949 Pearson (278) discovered the spectacular effect (unfortunately soon followed by a relapse) of A.C.T.H. (cortico-stimulin) (*) on acute leukemia (351). Cartwright (62, p. 295) established that the improvement effected by A.C.T.H. in cases of acute leukemia is accompanied by a return to almost normal levels of copper in the blood serum. When the relapse takes place, however, the copper content of the serum rises once more, as is clearly illustrated in Fig. 11 (p. 133). Before treatment the copper content of the patient is seen to have been above 320 $\mu\text{g. per cent.}$ (*) Treatment commenced on the sixth day, and within a very short space of time, towards the fifteenth day, the patient, on the basis of the disease symptoms (volume of red and white corpuscles, etc.), was regarded as cured. This cure was accompanied by a rapid fall in the copper content of the blood, which on the twentieth day was already almost normal (110-120 $\mu\text{g. per cent.}$).

The doses of A.C.T.H. were progressively reduced and finally stopped on the forty-fifth day. By this time, however, signs of a relapse were already obvious and the copper content of the serum was beginning to rise again. Administration of A.C.T.H. was resumed, but with no effect. The relapse was final, and parallel to the rapid aggravation of the patient's condition the copper content of the serum never stopped increasing.

Variations in the copper of the blood cannot be used for diagnosing cancerous tumours because similar increases are met with in all infectious diseases and even in certain non-pathological conditions, such as pregnancy. But Cartwright's experiment justifies the hope that this variation in the copper content of blood serum will aid assessment of the effectiveness and persistency of treatment for cancer, whether by radiation or by means of an anti-mitotic substance. (***)

(*) Or corticotrophic hormone secreted by the anterior pituitary gland (see p. 109).

(**) I.e., almost thrice normal.

(***) Arrests cell multiplication.

Why does the blood serum of the cancer patient become richer in copper ?

The same questions as were asked in the case of infectious diseases may be repeated in this context also.

(1) Why does the blood serum of the cancer patient become richer in copper and remain so as long as the presence of the tumour continues?

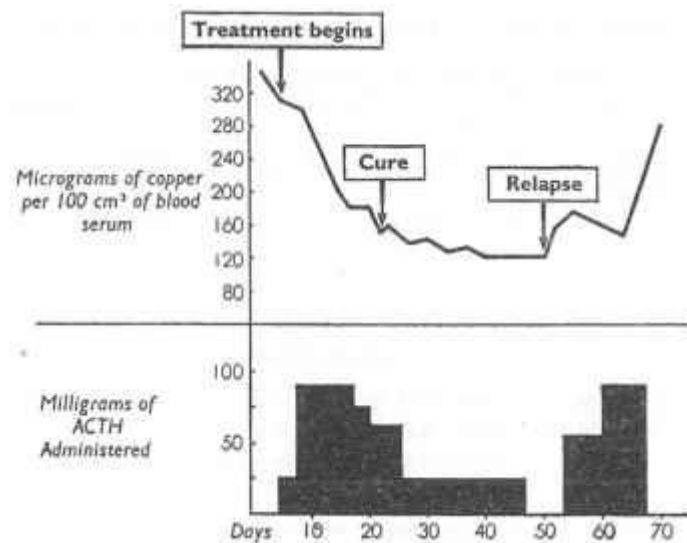


FIG. 11. Modifications in the copper content of the blood serum of a patient suffering from acute leukemia and being treated with cortico-stimulin (A.C.T.H.).

(N.B. The patient in question was male, 26 years of age.)

From Cartwright (62, p. 297).

(Drawing by Marthe-Rosine Voisin.)

(2) Why, when the tumour disappears (surgical removal or treatment of some kind), does the copper content return to normal, only to increase again immediately a relapse sets in ?

Fundamental role of catalase in cancer

Within an earlier hypothesis above I assumed that, in the case of infectious diseases, this sudden "mobilisation" of the copper in the

blood was necessary to accelerate the synthesis of catalase, an instrument of defence against microbial attacks. Surprisingly enough, the same hypothesis can be advanced in the case of cancer.

It will be seen later that in a patient suffering from a cancerous tumour there is a diminution in the catalase content of cancerous cells (p. 170) and of certain organs, such as the liver (see pp. 163-164). Surgical removal of a tumour has a twofold effect:

a *reduction* in the abnormally *high* copper content of the blood serum;

an *increase* in the abnormally *low* content of catalase in the liver.

Such a parallelism as this cannot but strike one.

It will be assumed once more, therefore, that the "general mobilisation" of copper in the blood serum of the cancer patient is aimed at speeding up synthesis of the heme of catalase, which also seems to play a decisive role against cancer.

Comparison of the variations in copper and properdine in blood serum

N.B. This chapter may be omitted by the non-specialist reader.

The three known mechanisms of non-specific defence

THREE important mechanisms (*) for the non-specific defence of the organism have already been referred to:

- (1) Phagocytosis.
- (2) Properdine system.
- (3) Copper (i.e. probably catalase).

Phagocytosis, of which nothing is known so far as cancer is concerned, will be left aside while the other two mechanisms are compared in infectious diseases and in cancer.

The reciprocal variations of properdine and copper in serum differ between infectious diseases and cancer

Both with infectious diseases and with cancer, the copper level in the blood serum always rises. By contrast, the variations in the properdine content are far from being homogeneous and regular in these two types of disease. Although these are not absolute rules, the properdine level *increases* in the case of fever and infectious diseases but *decreases* in the case of cancerous tumours (**) (see p. 56).

These *contrary* variations of copper and properdine in the two types of disease in question were confirmed by observations recently made (in 1957). It was found (55) that in the majority of infectious diseases involving inflammation there is a *simultaneous increase* in

(*) Fever is considered as a defence *reaction* accompanied by certain defence *mechanisms* which include the three listed.

(**) If cancer is caused by a pathogenic agent this in itself constitutes a difference between cancer and infectious disease that must be borne in mind.

properdine (*) and copper in the blood serum. In the case of cancerous tumours, on the other hand, an *inverse* relationship is observed: the properdine content of the blood serum *diminishing* while the copper content *increases*.

"General mobilisation" of copper for the purposes of non-specific defence is universal

"General mobilisation" of copper as a mechanism of non-specific defence appears to be more universal in occurrence, or at least more regular, than the mechanism involving properdine. Consequently, particular attention must be paid to maintaining conditions as favourable as possible to this "general mobilisation" process. This is one of the main objectives of "protective" medicine. The aim must be above all to maintain that *non-specific* immunity which has been described as natural immunity. It is more than twenty years since Alexis Carrel, the French Nobel Prize-winner, wrote:

"From now on medical science should be directed towards research into the various factors involved in *natural* immunity."

His cry seems hardly to have been heard and can only be repeated today. The important point is that it is becoming more and more clear, particularly in the case of copper, that this natural or non-specific immunity is strictly regulated by nutrition and by the *soil*.

(*) I.e., properdine *system*.

From the soil to virus diseases—via catalase

Virus—fugitive and variable element

ONE cannot honestly say that vaccination against foot-and-mouth disease has given complete satisfaction. I believe that one could express the same opinion about Man in relation to Asian 'flu or, indeed, to a simple head cold.

When I hear it said, "Virus A had become Virus C; now it has become Virus O; we must modify the vaccine in consequence", I get the impression that these viruses are mischievous gnomes playing abominable tricks on us.

From nucleo-protein to the molecule of virus

I think it is necessary, as for the other infectious diseases, to give more and more attention to the disturbance of certain metabolic mechanisms which render the cell open to the attack of these viruses. This is all the more necessary, as it is not certain, as we shall see, that the nucleo-proteins of the cells, of which the metabolism is disturbed, cannot themselves give birth to viruses (77).

The German Nobel Prize-winner, Butenandt, states:

"There exists a continuous chain coming from the molecules of protein to the normal molecules of viruses."

The most remarkable biological characteristic of virus is that they are without life, in the true sense of the word: they can live and reproduce only in a living organism.

Many researches of the Japanese scientist Yamafuji (417-426) and his colleagues have shown how a disturbance of the metabolism can cause the transformation of the nucleo-protein of the cell to the virus molecule.

These results seem to have received little attention and it therefore seems advisable to give a short resume of them.

Catalase protects the silk-worm against the polyedric virus

Yamafuji showed that the juice pressed from leaves of tobacco infected by mosaic virus had a lower content of catalase than the juice of healthy leaves.

The Japanese scientist made a similar observation on silk-worms affected by polyedric virus. He then made the following truly remarkable experiment: he added to a polyedric virus a certain quantity of catalase extracted from beef liver and he spread the virus (either pure or so treated) on the mulberry leaves which were eaten by two different groups of silk-worms. The number of worms infected by the virus was about 50 per cent in the group which had consumed the virus to which *catalase had been added*, relative to the number of worms affected in the group on the mulberry leaves with pure virus.

Hydrogen peroxide can transform molecules of the nucleo-proteins into viruses

Yamafuji therefore came to the conclusion that the virus molecule represents a pathogenic phenomenon due to a disturbance in the protein metabolism, generally resulting from penetration of the virus molecule into the living cell. It is equally possible, however, for a virus to appear naturally or artificially under the influence of factors that upset the metabolism of the proteins in the cell.

Yamafuji assumed the existence of a relationship between the physiological formation of hydrogen peroxide (*) and the polymerisation (or denaturation) of normal nucleo-proteins of low molecular weight, leading to the formation and multiplication of viruses.

Catalase activity is diminished in tissues infected by virus

In the course of the processes of biological oxidations certain amounts of hydrogen peroxide, a violent poison of the tissues, are always formed. It is immediately dissociated, however, in water and oxygen (**) by the enzyme catalase, which is widely distributed in the tissues. If, for some reason or other, catalase is not present or is inhibited, the result is fairly large quantities of hydrogen peroxide in the tissues.

Yamafuji studied the influence of viruses on catalase activity, and found that it was reduced in the following instances, for example:

(*) Or oxygenated water.

(**) See p. 112.

sugar-cane attacked by mosaic virus;
silk-worms affected by the polyedric virus;
tobacco leaves with mosaic virus.

To achieve the deficiency which will allow it to multiply, the virus "encloses" the catalase in its molecule, thus rendering the enzyme inactive.(*). If, thanks to this mechanism, the catalase is sufficiently reduced, then excessive production of hydrogen peroxide will take place in the cells.

Creation of virus experimentally by means of hydrogen peroxide

It remained to prove whether hydrogen peroxide could bring about the presence of a virus. Yamafuji (419) treated tobacco leaves with hydrogen peroxide and succeeded in creating a virus which was transmissible by inoculation. Another virus also developed (420) which was transmissible to silk-worms by feeding them with barium peroxide.

Hydroxylamine is known to be a powerful inhibitor of catalase and should therefore be able to bring about the presence of hydrogen peroxide in cells. Yamafuji succeeded in creating, experimentally, mosaic virus in healthy tobacco plants that he had treated with this chemical (419). Silk-worms receiving hydroxylamine in their food were attacked by polyedric virus disease (417).

Analogous results were obtained (421) with acetoxime, a condensation product of hydroxylamine and acetone. Potassium nitrite (KNO₂), which brings about an increase in the oxime content of the organism, can likewise start up virus diseases in silk-worms (422, 423, 424).

Yamafuji's results

The great volume of work carried out by Yamafuji and his co-workers over a period of more than twenty years has therefore shown that:

a virus disease reduces catalase content of the cells;
hydrogen peroxide can create viruses artificially;
catalase inhibitors, such as hydroxylamine, acetoxime and mineral nitrites, can likewise lead to virus formation.

(*) Yamafuji and his co-workers have unfortunately given no information regarding the mechanism by which the virus "encloses" or inhibits catalase.

Catalase and the virus of foot-and-mouth disease

Having studied Yamafuji's work, two Swiss veterinarians (347), in 1949, evolved the following argument: curious at first sight, it is true, but nevertheless not devoid of common sense.

The difference is smaller between a silk-worm and a cow, on the one hand, than between a silk-worm and a tobacco leaf, on the other. In other words, the difference between two individuals in the animal kingdom is less than between one individual in the animal and another in the plant kingdom. In the case of one virus disease in silk-worms and another in tobacco a *diminution of catalase* in certain cells was noticed. What is the effect of the virus of foot-and-mouth disease on the catalase in the blood of cattle? The Swiss workers injected foot-and-mouth disease virus into twelve cows. In only one animal was no reduction in the catalase activity of the blood observed; in all the others the diminutions in catalase varied between 10.9 and 53.8 per cent, with a mean of 24.8 per cent.

Due to experimental difficulties, the results obtained were unfortunately not always so clear-cut, (*) and the work, to my knowledge, was not continued.

Siliceous and granitic soils are unfavourable to foot-and-mouth disease

It is far from certain that the virus of foot-and-mouth disease reduces catalase activity in the blood. It is strange, however, to relate that, if reduction of catalase in the cells favours foot-and-mouth disease, this phenomenon would explain certain observations that have been made regarding the geographical distribution of the disease.

It was stated above (pp. 113-114) that copper deficiencies in the diet (and therefore in *the soil*) brought about catalase deficiencies in the blood or liver of animals.

In 1939 the German veterinarian Peters (281) presented to the Veterinary Association of Stuttgart a report on the geographical distribution of foot-and-mouth disease in Württemberg. He stated that on sandy, granitic, gneissic soils, etc., the percentage of animals attacked by foot-and-mouth disease did not exceed 10 per cent;

(*) These results are not clearly established because in Switzerland Moosbrugger (255, 256) later found different results.

On the other hand the numerous and repeated results of Yamafuji stand and his theory continues to be confirmed by recent work. However, a distinction must be made between catalase in the *cell* itself and in the *blood*.

whereas on soils with a fairly high content of lime the percentage was 35-40 per cent, sometimes even reaching 70-80 per cent in certain districts.

Equally interesting is the fact that the Assistant Director of Agricultural Services in the Loir-et-Cher region very recently told me that foot-and-mouth disease did not develop to any great extent on certain sandy soils in the Sologne area (centre of France). On the other hand, in maps of foot-and-mouth disease in France, the Finistere region, where granitic soils are widespread, is generally blank.

It is indeed remarkable that copper deficiencies are rather rare (*) on siliceous soils (180) and, to go back to the hypotheses previously advanced, it is possible that these soils do not cause catalase impoverishment and that animals consequently can resist attack by the foot-and-mouth disease virus.

The soil as a prophylactic element in virus diseases

All these studies and hypotheses open up horizons revealing great hopes for Man's prophylactic struggle against virus diseases. This prophylaxis is becoming all the more essential in view of the multiplication and constant self-modification of viruses and because the preventive (vaccines) or therapeutic (serum) methods available seem in some cases to diminish rather than increase in efficiency. "Protective medicine" is the answer if the fight against viruses is to progress.

(*) This, however, is not an absolute rule.

Catalase, a weapon of specific defence against Streptococcus hæmolyticus

Catalase in specific defence

CATALASE appears not only to play a universal part in non-specific defence: its role in the face of certain, definite, infectious agents can equally well be demonstrated. Before examining in detail the part played by this enzyme in tuberculosis, its participation in a special disease will be considered.

Periodic oral ulceration

An almost tragic incident, which occurred recently in a surgical operating-theatre in Japan, demonstrates the protective role of catalase against certain *specific* bacterial attacks.

In order that the implication of this incident may be understood it is first necessary to explain a special disease. There are few diseases more mysterious and more resistant to treatment than periodic oral ulcerations (ulcerative stomatitis). They may even become gangrenous, then penetrate to the nose and maxillary sinuses. Local applications of antibiotics are ineffective. The micro-organism predominant in these oral lesions is *Streptococcus hæmolyticus* (or *Streptococcus pyogenes*), which produces hydrogen peroxide. This bacterium occurs in the normal oral bacterial flora.

In the case of normal persons the hydrogen peroxide produced by this bacterium is destroyed by the catalase of the blood, and it cannot develop.

The catalase of the blood and the action of hydrogen peroxide

The catalase, as we know, decomposes the hydrogen peroxide.(*)
If hydrogen peroxide is added to *normal* blood there is an emission

(*) See p. 170.

of oxygen, and the colour of the blood remains normal. But if the blood is very impoverished in catalase, and a *little* hydrogen peroxide is added, its colour becomes brownish-black and there is no emission of oxygen. This coloration is due to the formation of methaemoglobin.(*)

If to this blood impoverished in catalase a *considerable* amount of hydrogen peroxide is added, the blood eventually becomes colourless. If to this colourless blood there is added a reducing agent, such as dithionate of sodium, a rose-coloured substance is formed called "pentdyopent" by the German scientist Bingold (43).

These indispensable preliminary ideas lead to the unexpected incident which occurred in the course of a surgical operation on oral ulceration.

Oxygenated water darkens the oral tissues of patients suffering from ulcerations

At the University of Okayama (Japan), Professor Takahara (367) operated on an oral ulceration in a young girl of eleven years. Her condition had become acute, the right nasal cavity contained a tumour and tissues in a state of putrefaction. The Japanese surgeon removed the tumour and asked his assistant to pass him the oxygenated water to wash the cavity. He was aghast at seeing the tissues become brown-black and cried: "You have given me silver nitrate instead of oxygenated water." The assistant hurried to identify the bottle. It was, indeed, oxygenated water. The evidence had to be accepted; the oral tissues of the young patient assumed a brown-black colour under the action of the oxygenated water.

Marked poverty in catalase of the blood of patients suffering from oral ulcerations

The studies then undertaken by Takahara demonstrated that the blood of patients suffering from these oral ulcerations was very poor in catalase, and sometimes even completely devoid of it.

The Japanese investigator showed that blood taken from the ear of these patients became blackish when a small quantity of hydrogen peroxide was added, and that there was no emission of oxygen. Takahara was able to reproduce the pentdyopent reaction of Bingold.

(*) Colouring matter arising from the action of oxidising substances on oxyhaemoglobin.

The lack of catalase in the blood and tissues allows a common bacterium to become pathogenic

The case of the oral ulcerations demonstrates a very important lesson. A common and harmless bacterium becomes pathogenic because the blood and the tissues have been impoverished in an enzyme, which is a means of defence against this bacterium.

The great merit of these Japanese observations is that they reveal the fundamental role of hydrogen peroxide and catalase in the struggle of the cells of the organism against a pathogenic agent, streptococcus haemolyticus. So long as the cells of the body are sufficiently rich in catalase, they can destroy the hydrogen peroxide "sprinkled" over them by the bacterium. If their catalase supply is impoverished, due, for example, to a copper deficiency in the soil (p. 114), they will succumb to the bacterial attack.

A study of tuberculosis will reveal even more plainly the role assumed by catalase in the struggle for life between cells, whatever their nature.

CHAPTER 35

*The great illusion of bovine tuberculosis
eradication by tuberculin testing*

Tuberculin

TUBERCULIN is an extract from a culture of the bacillus of tuberculosis discovered in 1890 by Robert Koch. Its history begins with disaster: Robert Koch believed that he had discovered a specific cure for tuberculosis, and this scientific error led to many deaths.

Tuberculin testing

Tuberculin testing consists of injecting a cow with tuberculin. It is believed that if the animal is tuberculous the injection will bring about a reaction, either local or general, depending on the method of inoculation used. If the animal reacts it is considered to be infected with the bacillus of tuberculosis.(*)

Milk from cows reacting to tuberculin

It was considered that milk from tuberculous cows could communicate tubercular infection to human beings: an infection generally expressed in extra-pulmonary forms, such as tubercular meningitis. Since, on the other hand, cows reacting to tuberculin are believed to be infected with the tuberculosis bacillus, it has been deduced that the milk from such cows could constitute a danger to Man(**) On the basis of these conclusions many countries subscribe to the elimination and slaughter of tuberculin reactors. Such a policy has cost Great Britain £3½m. In the five years between 1951 and 1956 Holland spent £6¾m. in slaughtering 400,000 cows that were

(*) This assumption has given, and still gives, rise to much controversy (410), but all are agreed that animals in an advanced state of tuberculosis do *not* react to tuberculin.

(**) Those conclusions are far from being generally accepted. Lung specialists, such as Rieckenberg (300), even go so far as to claim that milk from cows reacting to tuberculin confers on those who drink it a certain immunity to tuberculosis (243).

tuberculin reactors. This is what is known as systematic eradication of cows reacting to tuberculin. (*)

Tuberculosis, like all bacterial diseases, is a biological accident

It will be assumed here (**) that every cow that reacts to tuberculin is tuberculous, and that the milk from such cows can transmit tuberculosis to whoever drinks it. But even if these facts were true, and even if, by spending many thousands of pounds, one could succeed in eliminating tuberculin reactors, one still would not have progressed very far, in my opinion, towards a solution to the problem.

It is "environment" that makes animals tuberculous

If there is a high percentage of tuberculous animals on one farm and none at all on another, the reason is that the "*environment*" in the former case is favourable to the development of tuberculosis. The tuberculous cows may be eliminated, but *unless the conditions that are favouring the development of tuberculosis are altered*, a large proportion of the healthy stock bought in to replace the slaughtered animals will very shortly also fall victim to the disease.

In my capacity as President of the Federation of Dairy Farm Co-operatives of my district, I have seen for myself that when 30 per cent of a herd are revealed as reactors by tuberculin testing one may rest assured that this is not mere chance, but the result of an "*environment*" creating conditions favourable to the development of the bacillus of tuberculosis. One can also be certain of what will happen when the reactors have been eradicated: if the habitat, state of the soil and feeding conditions are not changed a high percentage of reactors will reappear in the herd, at a maximum, three years later.

Hartwig (146) has pointed out the same phenomenon in a herd from which all the cows reacting to tuberculin had been eliminated and replaced by non-reactors. Some months later a proportion of the new animals was reacting also. (***)

(*) The slaughter of such a large number of cows, often very high yielders, obviously raises the question of their replacement: a problem not easily solved, as the number of cows of quality is limited.

(**) But how many reservations should be made! I should like to see an accurate scientific experiment showing that a mouse or guinea-pig fed on milk from a cow reacting to tuberculin had been attacked by tuberculosis. If this were true for *raw* milk, would it still be true for *pasteurised* milk?

(***) Hartwig believes that this was due to the fact that the recently introduced animals were in fact tuberculous, although they did not react to tuberculin. I am convinced that this is not the explanation; and it is better that it should not be so, or what would really be the value of tuberculin testing?

The two environmental factors favouring tuberculosis

The environmental conditions on a farm which give rise to the development of tuberculosis are many, but they can be classified in two categories:

- (1) Unhealthy living conditions.
- (2) A diet deficient in quality and/or in quantity.

The first category will be dealt with briefly below and the second in the chapters that follow.

Unhealthy living conditions

Among unhealthy living conditions mention should be made firstly (246) of overheated, badly lit, badly ventilated housing. I am reminded here of a story often told by my old veterinary surgeon, the late Dr. Boissière:

Some forty years ago, after World War I, a rich industrialist in our district decided to go in for cows. At this time the view was held that if cows were to produce a lot of milk they must be housed in a fairly warm atmosphere. The industrialist's advisers therefore had him build a magnificent shed with *little* air, *little* light and a *lot* of heat. The herd consisted of bought-in cows, all of which, without exception, were non-reactors to tuberculin. Two years later more than a third of the cows were reacting and were sent for slaughter, being replaced by a purchase of non-reactors. But every time a periodic check was made, a high percentage of reacting cows was found, either among the last lot bought in or among a previous lot.

Cow-sheds and tuberculosis

Ultimately, they had to stop devoting their attention exclusively to the *consequences* and turn to studying the *causes*. It was thought that perhaps the housing conditions were not very hygienic, and so these were altered, with happy consequences for the health of the herd.

It is to the credit of the official French Veterinary Services that they have always wanted a proportion of the funds allocated for the eradication of cows reacting to tuberculin to be devoted, as part of a parallel and simultaneous policy, to the improvement of standards of hygiene on the farm.

Tubercular homes

To turn to human housing. It is well known that there are such things as unhealthy homes, true slums where whole families are attacked by tuberculosis. The inhabitants are not tuberculin tested (*) and the reactors sent to the slaughterhouse. The final result, however, is the same: before long the whole family will go to the cemetery. A new and healthy family takes up residence in the badly lit, badly ventilated house. Within a short time, it too falls victim to tuberculosis.

Tuberculosis, a disease of poverty

Tuberculosis specialists have never stopped repeating: "Contagion certainly does exist, but the fight against tuberculosis must not be directed solely against the bacillus itself, but towards maintaining a 'terrain' resistant to the bacillus. Poverty, overwork, privation, diabetes, etc., are rightly considered as predisposing towards tuberculosis."

Unfortunately, the research work which has been undertaken up till now has hardly been concerned at all with nutrition as a protection against tuberculosis.

When one systematically eradicates tuberculous cows (**) from a herd without paying any attention to the causes of the disease, one puts oneself in the same position as the veterinary surgeon who administers intravenous injections of magnesium to cows suffering from grass tetany without bothering to look into the reasons for the tetany (see p. 52). But if these causes are not eradicated, other cases of grass tetany will follow on the same farm. Similarly, if the causes of tuberculosis, human or animal, are not eliminated, the disease will continue to reappear.

The problem will probably be made more comprehensible by asking the following question.

Why do peaceful tuberculosis bacilli become dangerous ?

The lungs of each one of us are inhabited by millions of tuberculosis bacilli, which we manage to accommodate quite well. They live

(*) Winnigstedt (410), a director of the Association of German Animal Breeders, writes: "As Professor Wüstenberg has shown in human medicine, 'tuberculosis' must not be confused with 'reacting to tuberculin'. Men would tremble if they knew that everyone over fifty years of age reacts positively to tuberculin. But they may be reassured: this does not mean that they are tuberculous."

(**) I.e., reactors to tuberculin.

there very peacefully without delivering frenzied attacks against our cells. Why, then, do they suddenly thrust themselves upon one of our organs (most often the lungs) and make us into tuberculosis sufferers ?

As Kollath (191, p. 124) says:

"The bacillus does not explain tuberculosis. Almost everyone is infected by the bacillus, but everyone does not suffer from tuberculosis. The most important thing is not to know why people become tuberculous, but to discover why those who are carriers of the bacillus are not tuberculous."

Increased virulence or reduced powers of resistance?

There are two hypotheses possible for explaining the fact that a peaceful bacillus becomes dangerous:

1. The capacity for resistance of the cells has diminished.
2. The virulence (or pathogenic character) of the bacilli has increased.

If the possibility of these two alterations, either separately or simultaneously, is admitted, an explanation for them has still to be found.

As has just been said, attention, as in other diseases, has been devoted mainly to the therapeutics of tuberculosis, that is, to the struggle against the "consequences".

The "preventive" battle against tuberculosis, as against all diseases, has been conceived as early tracking down of tuberculosis lesions in Man by means of X-ray, analyses, etc., and in animals by the reaction to tuberculin testing. In other words, the aim has been to confirm "failure" at a very early stage and prevent matters proceeding along the road to bankruptcy.

The study of infectious diseases, so far as the chemical inter-relationship between organism attacked and pathogenic agent is concerned, is still in its infancy.

I am not certain that even a thousandth part of the funds, or a fraction of the pages in the reviews and proceedings of congresses on tuberculosis, are devoted to studying the two questions that have just been asked. If an answer could be given to them, we should perhaps be in a better position to develop "protective" medicine in this sphere.

In the light of the most recent discoveries, an attempt will now be made to understand these two phenomena, even if only in part.

CHAPTER 36

The endocrine system regulates an organism's capacity to resist tuberculosis

N.B. This chapter may be omitted by the non-specialist reader.

Hormones and resistance to tuberculosis

IN studying some of the factors determining the non-specific immunity of the organism mention was made (p. 107) of Selye's work at the University of Montreal (Canada) concerning the importance of the pituitary-adrenal system in the *general* and *non-specific* defence mechanisms of the organism. As Dubos (99) of the Rockefeller Institute states, all recent study has shown that susceptibility and resistance to infection by the bacillus of tuberculosis are liable, under the influence of hormonal factors, to far-reaching changes which take place rapidly and are easily reversible. Some of these hormonal influences on tuberculosis will now be examined.

Somatotropin increases resistance to the bacillus of tuberculosis

Selye (205, 329) has shown that cortisone (*) renders a normally resistant species of rat (*Albinos Wistar*) susceptible to infection by tuberculosis. But simultaneous treatment of these rats with somatotropin (secreted by the pituitary) exercises a markedly protective effect against tuberculosis, cancelling out the sensitizing influence of cortisone. From this the Canadian worker concluded that resistance of an animal to infection by the bacillus of tuberculosis is very obviously a function of hormonal factors.

This was subsequently confirmed with mice that had been contaminated with human tuberculosis bacilli. The mice belonged to a species particularly susceptible to the disease and had not been

(*) Steroid hormone secreted by the *adrenal* cortex.

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treated with cortisone to increase their susceptibility. *The finding was that somatotropin has a markedly protective effect against tuberculosis* (206, 207).

These investigations plainly demonstrate the protective role of one particular hormone (somatotropin of the pituitary) in *specific* defence against the bacillus of tuberculosis.

Professor Even's prudent conclusion

These findings have been confirmed many times over, but they have also been doubted: in France, for example (52, 107, 108). Professor Even, of the Faculty of Medicine in Paris, however, has picked out all the homogenous features from results that appear to be contradictory. He writes:

"The diversity of experimental results obtained with somatotropin may well be compared with that arising in the case of A.C.T.H. and cortisone. As with these hormones, moreover, reading of the records reveals variations of some magnitude in the conditions under which the experiments were carried out.

"The prudent conclusion, which appears to be legitimate in the present state of affairs, is that somatotropin exerts an *undeniable* influence over inflammatory reactions arising in the case of pulmonary tuberculosis: an influence which in the end may be either favourable or injurious. This property, and risk, is common to all the means of non-specific stimulation that have been applied in cases of tuberculosis."

Stress will be placed here on Professor Even's words: "Somatotropin has an undeniable influence on pulmonary tuberculosis."

Two hormones appear to have a contrary action on tuberculosis

But one fundamental piece of information emerges from what sometimes appear contradictory observations: two hormones, *somatotropin* of the pituitary and *cortisone* from the adrenal cortex, have a decisive influence on the resistance of the organism to tuberculosis.

On the whole and in the majority of cases it may be said that:

somatotropin *increases* resistance to the bacillus of tuberculosis;
cortisone *reduces* resistance to the bacillus of tuberculosis.

It is possible that the latter is a case of a *specific* action. This, however, does not appear to be highly probable, as this action on the part of cortisone has been observed with many other bacteria (182), and it has been seen (p. 107) that cortisone appears to considerably reduce

the capacity of phagocytes to *digest* the microbes ingested. It seems, therefore, that this is a *non-specific* action.

Through the thyroid, soil and nutrition affect the capacity to resist tuberculosis

As stated above (p. 108), it is becoming more and more probable that the hormones of the pituitary-adrenal system play an important part in the defence of the organism against all kinds of external attack. The close relationship between the thyroid and this system was pointed out. It can therefore be said that the thyroid (*) intervenes in the mechanism of defence against tuberculosis.

As no one denies that the functioning of the thyroid is strictly controlled by nutrition and by the *soil*, the conclusion may therefore be reached that soil and nutrition play a decisive part in tuberculosis resistance, even if only through the medium of the thyroid which exerts a profound influence over the hormonal secretions of the pituitary and adrenal glands.

(*) It appears, moreover, that relations between thyroid and tuberculosis may often be direct. In Poland in 1957 Maslinsky (233) drew attention to the many reciprocal relations between the thyroid and tuberculosis. He established that 36.8 per cent of those suffering from pulmonary tuberculosis showed enlargement of the thyroid, but was careful to emphasise that this percentage varies with geographical region and other factors. Maslinsky believes that in the initial stage of tuberculosis the bacilli emit toxic substances into the blood which stimulate the thyroid. In the case of chronic tuberculosis, growth of the connective tissue predominates, bringing about sclerosis of the thyroid ("*überwiegt das Bindegewebswachstum im Sinne einer Sklerosis der Schilddrüse*").

The action of bacteriostatic substances (antibiotic and chemotherapeutic) used against the bacillus of tuberculosis affect the metabolism of the hormones. They affect the thyroid in particular. From this Maslinsky concluded that, *through the medium of the thyroid*, different hormonal effects act on the developmental processes of tuberculosis.

CHAPTER 37

Virulence of the bacillus of tuberculosis is a function of its catalase content

Variants of tuberculosis bacilli resistant to isoniazide

OF all the chemical substances used against the bacillus of tuberculosis, isoniazide (*) appears to have given most satisfaction in the course of the last five years. It seems, however, that tuberculosis bacilli are capable of forming variants (**) resistant to isoniazide. Middlebrook and his co-workers in the Faculty of Medicine, Colorado (U.S.A.), were the first to show, in 1954, that variants of tuberculosis bacilli resistant to isoniazide *had lost a large part of their catalase activity*. For the most part the catalase activity of strains, which resist large quantities (50 mg.) of isoniazide, is absolutely, nil. (***)

The virulence of a tuberculosis bacillus augments with its catalase content

In America (71) and in Japan (427) it was found that cultures of tuberculosis bacilli resistant to isoniazide were not only low in catalase, but were only *slightly virulent* when injected into guinea-pigs and mice.

At the Tuberculosis Institute in Borstel (Schleswig-Holstein) in 1957, Meissner and Bönicke (238) studied systematically the relationship between catalase activity in tuberculosis bacilli and their resistance to isoniazide. They confirmed that there was a close correlation between the sensitivity of the bacilli to isoniazide and their catalase activity. The more resistant the bacteria to isoniazide, the lower their catalase activity. The two German workers *established the*

(*) Hydrazide of isonicotinic acid or rimifon.

(**) A variant is a colony of bacteria with qualities slightly different from those of the original colony from which it stemmed.

(***) Analogous and on the whole fairly similar results have been obtained by Desbordes (93) at the National Institute of Hygiene in Paris; Andrejew, Jacquet and Gernez-Rieux (13) at the Pasteur Institute in Lille, and Viallier (380) at the Pasteur Institute in Paris.

existence of a strict parallelism between the catalase activity of different strains of tuberculosis bacilli and their virulence in the guinea-pig. ()* All cultures with no or little catalase activity are attenuated in virulence. *Where catalase activity is greater the virulence of the strain is likewise increased.* This holds good for cultures of tuberculosis bacilli in cattle as well as human beings.

Resistance to isoniazide, reduced catalase activity and diminution of virulence are three hereditary characteristics of bacteria, but they do not necessarily always exist simultaneously. (**)

Reduced catalase activity in B.C.G. cultures

Cultures of B.C.G. (***) tuberculosis bacilli also showed reduced catalase activity, although the diminution is less marked than in cultures resistant to isoniazide. The important point, however, is that the difference is much more qualitative than quantitative.

As was shown by Bönicke (45) in 1958, the cause of the drop in catalase activity in cultures resistant to isoniazide is to be found in the fact that they are no longer capable of manufacturing the protein (****) that supports the heme (*****) of catalase, the protein and the heme together constituting the enzyme (see p. 111 for the two fractions of an enzyme). On the other hand, reduced catalase activity in B.C.G. cultures is due not to an irregularity in the synthesis of the protein supporting the heme, but to the fact that these colonies are no longer capable of synthesising the heme. The diminution of virulence in these two groups of cultures is due, therefore, to the destruction of different portions of the catalase.

Why the pathogenic character of tuberculosis bacilli increases simultaneously with their catalase content has still to be explained. With this end in view the phenomenon will now be shown in a more general light.

(*) Note that cultures of tuberculosis bacilli resistant to streptomycin and to para-aminosalicylic acid (P.A.S.) have a normal catalase activity (210). (Nothing is said of their virulence in guinea-pigs.) Nevertheless, in 1958 Hatta (147) confirmed that catalase activity of tuberculosis sputum allows perfect recording of the effectiveness of a treatment: if the treatment is effective, the catalase activity of the sputum decreases, but it remains unchanged if the treatment is a failure.

(**) At the Pasteur Institute in Paris, in 1958, Liberman (209) studied certain cultures resistant to isoniazide but nevertheless virulent in the guinea-pig and with a low catalase activity. These apparent contradictions result, as Meissner (238) noted, from a failure to observe three conditions: (1) exact definition of resistance; (2) elimination of all sensitive bacilli within the cultures studied; (3) adoption of a well-chosen inoculant.

(***) B.C.G. = bacillus Bilié-Calmette-Guerin, a tuberculosis bacillus of bovine origin rendered innocuous by various treatments and used as a vaccine.

(****) Or apoenzyme.

(*****) Or co-enzyme or prosthetic group.

CHAPTER 38

Catalase against hydrogen peroxide

Correlation between the virulence of many bacteria and their catalase content

THE relationship between bacterial virulence and catalase content is not peculiar to the bacillus of tuberculosis.

As long ago as 1929, Nungester (268) published his observations on the catalase activity of *Bacillus anthracis* (the anthrax bacillus). Rockenmacher (304), in 1949, found that virulence of *Pasteurella pestis* (the bacillus of plague) is a function of its catalase activity. Mention has been made earlier (p. 142) of the role of catalase in the periodic oral ulcerations caused by *Streptococcus hæmolyticus*. But the most extreme studies on this question have been undertaken in connection with *Brucella*.

The higher its catalase content, the greater the virulence of the bacillus of contagious abortion

In 1938 Merz (242), in Zürich, observed considerable catalase activity in the various types of *Brucella*: the bacteria that give rise to contagious abortion in animals and undulant (Malta) fever in humans. The fact that the virulence of *Brucellus abortus* increases with increasing catalase activity was confirmed by Huddleson (171) in 1943. He found that the *Brucellus abortus* of vaccine S.19, that is, a culture of very attenuated virulence, has a very low catalase activity. Finally, in 1956 Niznansky (267), in Czechoslovakia, confirmed that the higher their catalase activity, the more virulent the cultures of *Brucellus abortus*.

Two analogous phenomena which nevertheless appear to be contradictory

It appears, therefore, that, for many bacteria, virulence is a function of catalase activity. This may possibly even be a general rule.

Two symmetrical phenomena are thus present:

- (1) Several (perhaps all) bacteria are more virulent, the higher their catalase activity.
- (2) Diminution of the catalase content of the cells of a plant, animal or human being is accompanied by a reduction in their resistance to attacks by bacteria. (*)

Shell and armour

These two apparently contradictory phenomena require explanation, but it is only very recently that they have been observed at all, and so far as I am aware no written explanation of them is available as yet. I therefore venture to put forward my own hypothesis.

Two adversaries stand face to face.

- (1) They each fire the *same* shell—hydrogen peroxide.
- (2) They each protect themselves with the *same* armour—catalase.

Both seem to be "sprinkled" with hydrogen peroxide. The one who can produce the most hydrogen peroxide and at the same time is in possession of the best armour (catalase) will be the victor.

This hypothesis seemed plausible to me in view of the fact that leucocytes, the *blood* cells fighting against the *bacterial* cells, are known (see p. 103) to possess marked catalase activity. Nevertheless, I could not help regarding it as somewhat risky when one of my colleagues at the Veterinary College drew my attention to work which seemed to confirm the important role of hydrogen peroxide in the struggle for life between cells.

Hydrogen peroxide as an antibiotic

At the National Institute for Research in Dairying, Reading (Great Britain), Dorothy Weather (404) had found that lactobacilli isolated from Gruyère cheese produced a particularly powerful antibiotic which destroyed other bacteria in their vicinity. This antibiotic she named Lactobacillin. Subsequent work, however, in 1952 (405) led her to conclude that the substance was none other than hydrogen peroxide. (**)

(*) Or by virus, as seen in the case of Yamafuji's experiments (p. 138), of by cancer, as will be seen later (pp. 169-171).

(**) The strange thing is that the lactobacilli used did not appear to possess any catalase. Dr. Weather wondered why these bacilli were twenty-five times more resistant to hydrogen peroxide than their adversary (*Staphylococcus aureus*). The English scientist assumed that lactobacilli were capable of destroying hydrogen

The primary biochemical mechanisms invented by Nature are more or less the same in all living cells, whether bacterial or the cells of a human organ. One may therefore suppose that, in the struggle for life among cells, hydrogen peroxide represents the ordinary *offence* weapon, while catalase is a *select defence* weapon.

peroxide by means of a particular mechanism, already observed elsewhere in *Streptococcus faecalis*: this organism is capable of utilising hydrogen peroxide through the medium of riboflavin.

If this were confirmed, a new "armour" would come into being, allowing bacteria (and, more generally, living cells) to defend themselves when "sprinkled" with hydrogen peroxide. (For the catalase of lactobacilli see p. 169.)

CHAPTER 39

*Soil copper controls the catalase that plays
a fundamental part in the struggle for
life between cells*

**Catalase controls a cell's capacity for defence and power to
attack**

THE preceding chapters have illustrated the decisive role of catalase in:

- (1) *Non-specific* or *specific* defence of cells against microbial attacks (bacteria, virus, protozoa etc.).
- (2) *Power* of microbes to *attack*, their virulence apparently being a function of their catalase content.

The question arises why one cell fighting against another is richer in catalase than its adversary, a fact which allows it to survive while the adversary is destroyed.

One of the cells "neutralises" the catalase of the opposing cell

It has been seen that, in the case of viruses, Yamafuji (p. 139) supposed that the virus "enclosed" and neutralised the catalase of the host cell, thus preventing it from destroying the hydrogen peroxide. The latter polymerised the nucleo-proteins, forming new viruses.

Unfortunately, no information is available as yet as to how the virus "encloses" the catalase. But the fact that nothing at all is known of these biochemical phenomena (*) does not prevent the supposition that an analogous mechanism is to be found in all cells. The host cell could "enclose" the catalase of the bacteria, thus preventing the latter from becoming *virulent*. Conversely, the bacteria would be capable of "enclosing" the catalase of the host cell, depriving it of its capacity for *defence*.

(*) The large black circle of the unknown (see Fig. 1, p. 3) applies here.

**Impoverishment of the catalase in one of the cells to the benefit
of the opposing cell**

It may equally be supposed that catalase, or the elements necessary for its synthesis, is monopolised by one of the belligerent cells *at the expense* of its adversary. Kreis and Joubioux (194), of the Faculty of Medicine in Paris, emphasised in 1957, and with good reason, that the bacilli of tuberculosis can only increase their catalase content if the exterior milieu provides them either with the catalase or *the elements necessary for its synthesis*. It is possible, therefore, that this increase in catalase on the part of the bacillus is achieved at the expense of the catalase content of the host cell, or vice versa.

Copper regulates the catalase content of the cells

Light will be thrown on all these hypotheses in the future, and the development of this disequilibrium between catalase content of the cell of the attacking *bacteria* and that of the host *cell*, which is defending itself, will be explained.

Our business here is to find out how the soil influences the capacity for resistance to microbial attacks of both Man and animals. It will be remembered that synthesis of catalase is strictly regulated by copper (see p. 111) and that iron enters into the composition of the catalase molecule. It is also known that when the cells of the organism are attacked by microbes "general mobilisation" of the copper in the blood ensues (see p. 125). The hypothesis was advanced that the aim of this "mobilisation" is to allow increased and more rapid synthesis of catalase from the iron, and consequently to strengthen the capacity of the cells attacked to defend themselves.

A deficiency of copper in the soil gives rise to catalase impoverishment of the cells of the organism (see Fig. 9, p. 114). Moreover, it was shown that the amount of copper available in the soil is greatly influenced by the agronomic methods employed (see pp. 35-38).

**A "dust" in the soil plays a principal part in non-specific
immunity**

To summarise, the copper in the soil exerts very strict control over the quantities of catalase present in the cells, catalase being an element which determines the *virulence* of the microbe or the capacity of the organism for defence. Future research will show how a deficiency

of copper (or iron) can favour catalase enrichment of the bacteria at the expense of the host cell.

The following facts, however, are established:

(1) Catalase plays a fundamental part where mechanisms of *defence* and *attack* in infectious diseases are concerned.

(2) Catalase is controlled by the "dusts" of the soil, particularly copper.

CHAPTER 40

*If bovine tuberculosis eradication is to cease
to be an illusion*

Why do the bacilli of tuberculosis become pathogenic ?

AFTER the general considerations of the preceding chapters one is in a better position to answer the question asked at the end of Chapter 35 (p. 148). "Why do the tuberculosis bacilli that used to live peacefully in our lungs suddenly become a dangerous enemy, turning us into tuberculosis sufferers?" The question could equally well be put in another form:

Why has the resistance of our cells diminished?

Why has the virulence of the tuberculosis bacilli increased?

The fundamental question which must ultimately be asked is therefore:

What part do soil and nutrition play in this diminution of the *resistance* of the organism or in this increase in the *virulence* of the bacilli?

The three reasons why the bacillus of tuberculosis becomes dangerous

It is now known that the bacillus of tuberculosis can become a danger as a result of the following three circumstances:

(1) The hormones of the endocrine system (see p. 150) assume a dominant role in the capacity of the organism to defend itself against the tuberculosis bacillus. The activity of this system is dependent on the functioning of the thyroid.

(2) The capacity of an animal (or human) cell for resistance is a function of its catalase content, which depends on the mineral matter in the soil and in the diet.

(3) Virulence of the tuberculosis bacillus is likewise a function

of its catalase content. Disequilibrium between the catalase content of the cell of the *bacillus* and that of the cell of the *animal* (or human being) can initiate the disease.

Nutrition, and therefore the soil, control the first phenomenon through the medium of the thyroid, (*) and the last two phenomena through iron and particularly through copper. (**)

Measures which must accompany the eradication of cows reacting to tuberculin

In describing "the great illusion of bovine tuberculosis eradication by tuberculin testing" (see p. 145) some (though not many) of the reasons why environment favours the onset of tuberculosis were discussed. We now understand that soil and nutrition can help to reduce the cow's capacity for defence or (and) increase the strength of the attack by the bacillus. Systematic eradication of cows reacting to tuberculin must therefore be accompanied by amelioration of living conditions (see p. 147), but above all *by improvement of the diet and of the soil*. Deficiencies not only of phosphate and calcium (***) but also of the trace elements must be systematically investigated.

As was stressed above (see p. 25) analyses of the soil and foodstuffs alone will not provide the answer. It is of paramount importance that the analyses relate to the animal: blood, skin, liver, urine, faeces, hair, etc. Only on this condition will tuberculin testing and systematic eradication of reactors cease to be an illusion.

(*) Only this point is referred to, but it is probable that there are many other *direct* influences of feeding and the soil on the endocrine glands.

(**) Not to mention the possible influence of other "dusts".

(***) These are generally the only two deficiencies ever quoted.

CHAPTER 41

Catalase, hemes and cancer

Catalase in the liver of patients with cancerous tumours

THE preceding chapters have demonstrated the fundamental role of catalase in the struggle for life among cells. It is noteworthy that, in the case of cancer, the catalase of one organ at least, the liver, (*) is subject to variations parallel to the development of the tumour, whatever the organ affected by that tumour. This is shown in Table 30, below, from which it will be seen that the catalase content of the

TABLE 30

Variation in liver catalase with different kinds of tumour

	Activity of the catalase of the liver
Normal liver	20.0
Hepatoma (primary cancerous tumour of liver)	1.0
<i>Transplanted tumour:</i>	
Hepatoma 31	0.0
Jensen sarcoma	0.0
Epithelioma	0.0
Liver of rat suffering from a natural tumour other than of the liver	2.0

N.B. These are mathematical units.

From Greenstein (135, p. 350).

liver is extremely low, or non-existent, in the case of primary cancer of the liver, or of tumour of any organ, whether transplanted or natural. Subsequent research was to confirm this reduction of the catalase in the liver in all sufferers from cancerous tumours, whatever the tumour or whatever the organ affected by that tumour.

(*) But very probably that of other organs also, and especially that of the cancerous cells themselves (see pp. 169-170).

The catalase activity of the liver returns to normal on removal of the tumour

Two facts are particularly interesting:

- (1) Diminution of the catalase activity of the liver proceeds closely with the development of a tumour in some organ of the body.
- (2) The influence of the tumour is reversible. If the tumour is eliminated, by surgical removal, for example, the catalase activity of the liver returns to its normal level. If a new tumour develops, the activity begins to diminish once more.

Tumours discharge into the blood the toxohormone that reduces the catalase activity of the liver

Japanese research workers, in a group headed by Fukuoka and Nakahara, have succeeded in extracting from tumours in humans (or in animals) a substance which, when injected into mice, *causes the catalase content of the liver to fall*, in exactly the same way as if these animals were suffering from a tumour (124). They have named the product toxohormone and have proved that it is discharged into the blood by the tumour.

The urine of tumour sufferers (262) also contains toxohormone.

The toxin excreted by a cancerous tumour can inhibit catalase and heme enzymes in several organs

In a parallel study at the University of Vienna (Austria) in 1955, Frisch-Niggemeyer (123) found that boiled tumour extract (*Kochsaft*) taken from the Jensen sarcoma of the rat, exercised an inhibiting action on the catalase of the red blood corpuscles of the horse as well as on the catalase of the leucocytes in human blood. From this he concluded that not only the catalase of the liver, but that of other organs also, is sensitive to the toxin. (*)

Toxohormone inhibits synthesis of catalase

Fukuoka (124) has stressed that the action of toxohormone on the catalase of the liver is not *direct*, either by functional inhibition or by destruction. The Japanese scientist was able to prove that toxo-

(*) Which is probably identical with the Japanese workers' toxohormone, although this is not certain.

hormone *inhibited the synthesis of catalase*, probably by impeding synthesis of the heme which contains iron and forms the active (prosthetic) group of this enzyme (see p. 112).

An attempt will now be made to examine more closely this mechanism that has become disordered.

Porphyrin metabolism is disturbed in the patient with a cancerous tumour

During the years 1956-57 Sugimura, Umeda and Ono (274, 275, 276, 360) pursued their investigations at the Cancer Institute in Tokyo, greatly advancing the knowledge available on disturbances arising in the organism due to toxohormone *secreted by every cancerous tumour*. They found that the level of free porphyrin (*) in the red blood corpuscles is higher in the patient with a cancerous tumour. They also determined a considerable increase in the free protoporphyrin in the liver, indicating that this organ was no longer capable of usage for synthesis of the heme. The conclusion reached was that, in every sufferer from a cancerous tumour, there is a "porphyric state", (**) particularly in the liver, due to secretion of toxohormone by the tumour.

Catalase impoverishment of the liver of the cancer patient is due to the breakdown of heme synthesis

These Japanese observations on the general disturbance of porphyrin metabolism in the cancer sufferer developed and confirmed certain earlier findings which had given an indication of this phenomenon.

In 1943 Auler (23) had noted increased porphyrin secretion in men and animals suffering from cancerous tumours.

Bingold (44) in 1951 observed that cancerous tissues are very low, or even completely lacking, in porphyrins, from which he concluded that the synthesis of tetrapyrrole rings (***) in such tissues is greatly diminished. He was of the opinion, moreover, that the lack of porphyrin in the tissues of malignant tumours is in agreement with Von Euler's (105) finding of a reduction in the catalase content (****) of

(*) Organic element involved in the composition of the heme and consisting of four pyrrole rings.

(**) In 1956 Ono (275), in the course of his investigations on the metabolism of rats with tumours, demonstrated a considerable increase in the excretion of coproporphyrin in the urine of these rats: this is adequate confirmation of their "porphyric state".

(***) Principal fraction of the porphyrins.

(****) As well as in the content of cytochrome c (see pp. 180, 181).

cancerous tissues. In Bingold's opinion, as well as that of the Japanese research workers, this catalase deficiency is due not to a lack of iron or protein, *but to a defect in the formation of the heme molecule*, resulting from a disorder in the metabolism of the porphyrins. (*)

These preliminary views on the disturbance of heme synthesis in cancer sufferers will help the reader to understand better the abnormal respiration mechanism of the cancerous cell.

(*) One must distinguish clearly between the disturbance of porphyrin metabolism in the cancer sufferer and that occurring in diseases grouped together under the name porphyrinuria. The latter is characterised not only by the excretion of large quantities of porphyrins in the urine but also by the formation of *abnormal* isomeric porphyrins of Type I (normal porphyrins are of Type III).

In the case of the cancer patient it is a matter not of abnormal synthesis but of cessation (or slowing down) of the synthesis of the normal series III as well as of the abnormal series I (44).

CHAPTER 42

Special mode of respiration in the cancerous cell

The respiration of the cancerous cell ceases to be normal

I SHOULD have liked to go into detail about the admirable and unusual work carried out by the Nobel Prize-winner Otto Warburg (394, 403) on the respiratory mechanisms of the cancerous cell. For thirty years this brilliant German scientist was constantly at work, perfecting his theory with a continuity of ideas that is truly exceptional.

It is enough to say that, according to Warburg's theory, cancer can have thousands of causes: tars, X-rays, radio-activity, carcinogenic substances in foodstuffs, pressure on the organs, etc. But all of these end up in one final, primary action: the *irreversible* disturbance of cell respiration.

The cell adopts a cancerous "way of life" in order that it may survive

The cell whose normal respiratory mechanism has broken down *beyond repair* will try, in order to survive, to create (*) a different method of respiration, "lactic respiration", also called "lactic fermentation" or glycolysis. By adopting this "way of life" the cancerous cell will be able to obtain for itself the energy that is necessary if it is not to succumb.

Despite a mass of research work, the mechanisms of the cell respiratory system whose breakdown has given rise to the cancerous "way of life" have not yet been determined. It seems probable that there may be one or several points affected in the respiratory mechanism or in the transmission of energy created by respiration.

(*) More exactly "to develop" for it is already in existence, although in slight degree, in a normal cell.

Disturbance of the synthesis of hemes in patients with cancerous tumours

Reference will be made later (see p. 178) to different possible causes of breakdowns in the transmission of respiratory energy, but so far as respiration itself is concerned, the recent research mentioned in the previous chapter seems to reveal one point very clearly: namely, that in the cancer patient, synthesis of the hemes that make up many respiratory enzymes, catalase and cytochrome oxidase (*) in particular, is disturbed.

A deficiency of iron (an element of the heme) is not excluded. But it has been seen (p. 164) that Japanese research workers came to the conclusion that metabolism of the porphyrins, organic fractions of the heme, was disturbed in the cancer patient. Deficiency of copper likewise disturbs heme synthesis, this being expressed, for example, in a deficiency of catalase (see p. 111) or cytochrome oxidase (see pp. 178-179).

One cannot but be impressed by the parallelism existing between disturbance of heme synthesis in the organism due to:

deficiency (direct or indirect) of copper;
the presence of a cancerous tumour.

This does not necessarily mean that the second phenomenon is a consequence of the first, but the parallelism is such that it merits attention. Several chapters will therefore be devoted to its study, leading to very disquieting conclusions on the copper metabolism disturbances that accompany cancer. First of all, however, Warburg's work, carried out in 1957-58, on some of the effects of low catalase content in the cancerous cell will be described.

(*) Naturally also the cytochromes (pp. 180-181).

CHAPTER 43

*Cancerous cells are more sensitive to X-rays
than normal cells because they contain
less catalase*

N.B. This chapter may be omitted by the non-specialist reader.

The cancerous cell is a partial anaerobic organism

As has just been explained above, a cancerous cell is a cell in which the energy is no longer provided by the normal respiratory mechanisms, but by lactic fermentation (see p. 167). As a result it must be regarded as a partly anaerobic (*) cell.

The aerobic organism loses its catalase in adapting itself to the conditions of anaerobiosis

It is a known fact that when lactic bacteria are cultured under anaerobic conditions their respiratory enzymes, particularly their catalase, are progressively destroyed. If these bacteria are subsequently brought into contact with oxygen they utilise the latter, by means of their yellow ferments (with riboflavin), thus producing hydrogen peroxide (H_2O_2), which in turn kills them, since they have no catalase left to destroy it. But if catalase (**) is added to these cells the hydrogen peroxide is rapidly destroyed and the cells remain alive in their contact with oxygen.

(*) An anaerobic organism is one which lives in the absence of free oxygen (gaseous or in solution). It should be noted that fermentation is looked upon in some quarters as "anaerobic respiration".

(**) Protection of anaerobic micro-organisms against oxygen by addition of catalase was discovered by Avery (24) in 1924. Then in 1933 at Dahlem, Warburg (396) discovered the chemical mechanism of hydrogen peroxide formation by anaerobes through re-oxidation of the yellow ferments.

The cancerous cell is low in catalase

The catalase content of the cancerous cell has frequently been a subject of discussion. It seemed natural that, being partially anaerobic, it should possess less catalase than the normal cell. The low catalase content of the cancerous cell had been pointed out by the Swedish Nobel Prize-winner, von Euler (105) in 1942 and was confirmed by Warburg (398) in 1953. More generally the latter noted that the cancerous cell had lost a proportion of its respiratory enzymes with iron (*Eisenfermente*).

X-rays create hydrogen peroxide in aqueous media

In 1944 Weiss (407) showed that X-rays create hydrogen peroxide (*) in aqueous media, and therefore in living cells.

The following three facts are, therefore, to be considered:

- (1) The cancerous cell is low in catalase.
- (2) X-rays create hydrogen peroxide in living cells.
- (3) Hydrogen peroxide is fatal to the cell if not immediately destroyed by catalase.

On this basis it is understandable that cancerous cells are more sensitive (**) than normal cells to the destructive action of X-rays, being poorer in catalase and therefore limited in their capacity to destroy the hydrogen peroxide created by these rays.

New therapy to make X-rays more effective

In 1958 Warburg (403) confirmed this result, and from it he tried to draw the following therapeutic conclusions.

Although cancerous cells are rapidly destroyed *in vitro* (under laboratory conditions) by very small amounts of hydrogen peroxide,

(*) This action on the part of X-rays stems from the combination of -OH radicals of primary formation, or from the reduction of molecular oxygen by -H atoms of primary formation.

(**) In his 1957 and 1958 investigations Warburg never mentioned the question of properdine (see p. 105), although the blood of the cancer patient is lower in the "properdine system". On the other hand, Pillemer (282, 306) and his co-workers observed that X-rays lower the properdine content of the blood. It is a known fact that total irradiation causes severe bacteriaemia. The American worker attributed this disappearance of general, *non*-specific resistance to bacterial attacks to the reduction of properdine in the blood. He proved his theory by administering intravenous properdine injections to irradiated animals: the resistance of these animals to bacterial infections was greatly increased as a result.

It would obviously be interesting to know what influence the action of X-rays, which accentuates properdine impoverishment, can have on cancer patients who are already impoverished with regard to properdine.

a cancerous tumour cannot be destroyed in the organism (for example, an ascites tumour (*) in the abdominal cavity) by means of hydrogen peroxide injection. Indeed, this therapeutic method is of no avail, for the blood that irrigates the tumour still contains sufficient catalase to destroy fairly rapidly the hydrogen peroxide injected.

Warburg (403) therefore proposes that the blood circulation *in the region where the tumour is situated* should be separated off from the general circuit and nourished by plasma pumped by means of an artificial heart. The cancerous cells would then receive no more catalase from the blood, and would be destroyed by the action of X-rays in the body itself as surely as they are destroyed in the laboratory.

Anti-cancerous effect of hydrogen peroxide in drinking-water

It is interesting to compare with these observations of Warburg in 1958 another treatment used by Holman in 1957 at the Welsh National School of Medicine in Cardiff. Following upon his preliminary studies of long forms of bacteria (166a), Holman advanced the hypothesis that disequilibrium between catalase and hydrogen peroxide could play a part in the formation of cancerous tumours. He had in mind the more or less encouraging results obtained with intra-peritoneal or intravenous injections of hydrogen peroxide into animals suffering from cancerous tumours. It was his belief that these injections were defective in that they did not allow the hydrogen peroxide to act *continuously*. To achieve this continuous and prolonged administration he adopted the most simple, one might almost say ultra-simple, method of all—adding oxygenated water to drinking-water (166b). He investigated the optimum proportion of hydrogen peroxide in drinking-water consistent with effectiveness but without running the risk of damage to normal cells.

Having ascertained this optimum, Holman offered drinking-water with the requisite proportion of hydrogen peroxide added to rats suffering from adeno-carcinoma tumour Walker (256) (which had been inoculated). The result is truly unexpected: a 50-60 per cent cure. The time required for the destruction of the tumour (in the rats cured) varied from fifteen to sixty days.

Carrying his boldness still further, Holman administered drinking-water with hydrogen peroxide added in the same proportion to four people suffering from inoperable cancerous tumours. In two of the cases the result was an obvious clinical improvement with diminution of certain biochemical characteristics reflecting the gravity of the tumour.

(*) Accumulation of liquid in the peritoneal cavity.

If these results were confirmed, a horizon full of hope would be opened up.

To prevent catalase impoverishment of the cell

The future will tell what possibilities are contained in these new and original treatments, which, however, are not lacking in complications and dangers.

These *therapeutic* methods make use, it is true, of the fact that the cancerous cell is impoverished with regard to catalase. But the method most likely to solve the problem of cancer is to ask *why* the cancerous cell is lacking in respiratory enzymes with iron, particularly catalase, and to try to *prevent* this impoverishment taking place. This is the aim of "*protective medicine*", and to it several chapters will now be devoted. First of all, however, two aspects of the role of catalase remain to be studied.

Catalase in the Bikini algae

Radio-active radiation, like X-rays, destroys cells by creating in them large quantities of hydrogen peroxide. The result is carcinogenic effects, or even death.

In the course of the first atom bomb test at Bikini the sea, in certain places, was rendered highly radio-active for several years subsequently. Nevertheless, many algae were seen to survive in these parts, a fact which gave rise to some surprise, and more so as they did not present any apparent anomaly. Analyses of the enzymes of the plants, however, revealed their secret (118, p. 237): their cells contained six times more catalase than normal algae. They had succeeded in adapting themselves to their environment by multiplying within their cells the catalase that made possible the destruction of the excess hydrogen peroxide created by the excess radio-activity in the water.

The soil, the first weapon of defence in a future atomic war

It is known, thanks to grass, that certain deficiencies in the soil (see p. 29) and in the diet upset the metabolism of animal cells and give rise (p. 111) to a low catalase content in these cells. By impoverishing the cells in catalase, therefore, these soil deficiencies will make them more sensitive to the radiation of atomic bombs, thus increasing the sphere of action of such radiation.

For all time the soil will remain the very basis of our life, in every sense of the word and from all points of view.

Cancer is less common at high altitudes because the Mood is richer in catalase

Frequency of cancer diminishes with altitude

THESE recent studies by Warburg on the low catalase content of cancerous cells should be compared, in my opinion, with some highly original Japanese investigations.

At the School of Medicine of the University of Nagoya (Japan) Oshima (276a), in 1956, carried out surveys and worked out many statistics showing that cancer in Man (*) is less frequent at high than at low altitudes. These statistics concerning human beings were confirmed by a similar result in the case of fowls: frequency of cancerous tumours in hens diminishes with altitude.

The carcinogenic power of butter yellow decreases at high altitudes

These statistical results were confirmed experimentally with transplantable sarcomae in fowls: these developed much less successfully at a high than at a low altitude.

But the most striking experiment was carried out in the course of investigations on the carcinogenic effect exerted on the liver by butter yellow (**) added to the diet of rats (see p. 183). The carcinogenic action of butter yellow was studied in two groups of rats:

one group was placed at the "Research Station for High-Altitude Medicine", situated on Mount Norikura, 9000 feet [2800 m.] above sea-level with an atmospheric pressure of 21.6 inches [549 mm.].

a second group at the University of Nagoya, which stands at a

(*) It is strange that in his work *The Geography of Cancer*, Steiner (348) does not take altitude into consideration in his statistics. I know of no other statistics concerning cancer frequency as a function of altitude, apart from the Japanese work mentioned.

(**) I.e., *para*-dimethylamino azobenzene.

low altitude where the atmospheric pressure is 30 inches [758 mm.].

The two groups received identical rations containing butter yellow in the same proportion. The results were as follows:

at the low altitude 92.9 per cent of the rats had cancer of the liver;

at the high altitude only 44.4 per cent, i.e., less than half, were affected.

The Japanese workers concluded that a high-altitude environment has an inhibiting action with regard to the carcinogenic effect of butter yellow.

Blood catalase increases at high altitudes

It remains to explain why a high altitude is unfavourable to the development of cancerous tumours. Oshima and his co-workers give no explanations,*) but I wonder whether the explanation for the Japanese observations is not provided by the investigations carried out by a Russian scientist Alexeeff (7, 8, 9) some thirty years previously on the high plateaux of Central Asia. What he found was in fact that *at high altitudes human blood is richer in catalase*.

If one assumes, as appears probable, that catalase is one of the elements of defence against cancer, then Alexeeff's findings throw a great deal of light on the Japanese statistics and experiments namely: a high-altitude environment develops resistance to cancer because it increases the catalase content of the blood.

(*) They have simply indicated that the high altitude was able to act favourably on the pituitary and adrenal glands, without specifying the nature of this action.

Catalase, virus of cancer and disturbance of cell respiration

N.B. This chapter may be omitted by the non-specialist reader.

Are Oberling's theory of viruses and Warburg's theory of respiratory disturbance opposed to one another?

THE question of whether or not cancer is caused by a virus can only be touched upon here. What is certain is that in animals at least certain cancers (especially different leukemias or leucosis) can be transmitted by viruses, or, to be more exact, by "particles" that behave like viruses (95).

The theory of the cancer virus was developed by the great French scientist Oberling (269). Personally I do not think that it is necessarily opposed to Warburg's theory, although the latter has always been strongly opposed to the theory of a cancer virus. An attempt will now be made to establish a correlation between the theory of respiratory disturbance put forward by Warburg and the virus theory initiated by Oberling.

The virus of leucosis in poultry upsets an essential mechanism transmitting the energy furnished by respiration

In 1954, at Duke University in North Carolina (U.S.A.), Mommaerts (250, 251, 252) and his co-workers made an observation which, to my mind, must alter many of our ideas not only on cancer but also on viruses.

Up to this time it had been very difficult to determine enzymatic activities in viruses. Mommaerts set about studying the virus of erythro-myeloblastic leucosis in poultry, a form of "blood cancer" so widespread in occurrence today among breeding flocks of poultry that it is doubtful whether there is a single flock in existence that is completely free from it.

The investigations at Duke University succeeded in proving that the infectious particles of virus had a highly developed enzymatic capacity for the dephosphorylation of A.T.P. (adenosine triphosphate), which transmits to the cell and to the organism the energy created by respiration. In other words, a virus that transmits and causes a cancer (leucosis of poultry) possesses an enzymatic activity that uncouples respiration and energy in the cell. According to Warburg's theory of a respiratory disturbance in the cancerous cell, this *uncoupling* of respiration and energy is a matter of great importance.

Mommaert's observations, if they can be confirmed, allow one single theory to be evolved from the theories advanced by Oberling and Warburg. This, it should be emphasised, is a personal assumption of my own.

Lack of catalase in the cancerous cell can lead to the spontaneous appearance of a virus

This relationship between viruses and the disturbance of respiration in the cancerous cell was to be seen in quite a different and very original light by the German scientist Seeger (327). His hypotheses, linking up the question of viruses with the respiratory disturbance in the cancerous cell, have the advantage of showing that the point of departure for cancerisation of the cell is catalase impoverishment; that is, a respiratory heme enzyme whose importance in the struggle for life between cells and in the development of cancer has frequently been stressed here.

Seeger started from Yamafuji's theory, which has been described above (see p. 138) and reasons as follows. Assume with Warburg that the many causes of cancer all end up in one and the same result: disturbance of the respiratory mechanisms of the cell. One of the fundamental elements in these disrupted mechanisms is catalase impoverishment of certain cells. This, it is known, will correspond with increased production of hydrogen peroxide, which will denature and polymerise the nucleo-protein molecule, making from it a virus molecule which, in order that it may multiply, will "enclose" and neutralise the molecules of catalase, thus transmitting cancer.

From the virus to the cancerous cell

The following phenomena thus appear in succession:

(1) Any carcinogenic action (tars, foodstuffs, radiation, etc.) disrupts the respiratory mechanisms of the cell. More par-

ticularly, synthesis of the hemes is disturbed, causing certain cells in the cancer patient to become impoverished with regard to catalase.

(2) This insufficiency of catalase gives rise in the cell to overproduction of hydrogen peroxide which will "denature" the nucleo-proteins, transforming them into viruses (or at least into particles that behave like viruses).

(3) If transported to another organism these virus molecules created in the cancerous cell will be able, by means of a similar phenomenon in the opposite direction, to reduce the catalase content of certain cells in that organism, thus upsetting their respiratory mechanism and forcing them to adopt the cancerous "way of life" in order to survive.

Seeger has completed and consolidated this very original theory by the addition of various other considerations.

The close bond between the virus of cancer and disturbance of the respiratory mechanisms of the cancerous cell is thus manifested.

CHAPTER 46

*Respiratory mechanisms disturbed in the
cancerous cell and upset also by copper
deficiency*

N.B. This chapter may be omitted by the non-specialist reader.

Cytochrome oxidase "sets" the electron on oxygen

THE cell has probably several different respiratory mechanisms indicating that there are several routes which can carry hydrogen to oxygen, enabling it to combine with oxygen and thus form water or hydrogen peroxide. In more scientific, and in more general, terms it may be said that there are several different methods of transporting the electron of the oxidised substratum to oxygen.

In its last stage the respiratory route, which is apparently the most important, utilises an enzyme which Warburg called "respiratory ferment" and which today bears the name cytochrome oxidase. This enzyme "sets" the electron on the oxygen molecule.

Cytochrome oxidase contains iron and copper

Cytochrome oxidase is a highly complex substance. From Warburg's experiments in 1928 (394) it is known to contain iron, part of which is in heme form. In 1938 Keilin and Hartree (184) put forward the opinion that cytochrome oxidase contained copper: an opinion either disputed or forgotten for twenty years. It was not until 1956 that Green (134), at the University of Wisconsin, was finally able to prove that cytochrome oxidase did contain copper, as indeed do the majority of, if not all, oxidases.

**Cytochrome oxidase content of the liver is greatly
diminished by copper deficiency**

In 1934 it had been discovered by Cohen (69) that a ration deficient in copper diminished cytochrome oxidase in the tissues of rats. When copper was added to the ration the cytochrome oxidase activity of the tissues very obviously increased again.

This experiment with rats was repeated five years later by Schultze, (*) attention being concentrated in this case on the cytochrome oxidase in the liver (321). Table 31 shows that after several weeks of a diet deficient in copper the cytochrome oxidase activity of the liver fell to one-seventh of the normal. A very small supplement of copper in the ration was sufficient to make the activity rise again rapidly to three-quarters of the normal.

TABLE 31

*Influence of copper deficiency on the cytochrome oxidase in
the liver*

Ration	Interval since weaning (in weeks)	Cytochrome oxidase activity of the liver
Normal		142
Copper deficient (Milk + 0.5 mg. iron/day)	2-3	60
	4	50
	6-9	19
Partly copper deficient (Milk + 0.5 mg. iron/day + 0.05 mg. copper/day)	6-9	98

N.B. Cytochrome oxidase activity is measured with an artificial unit and is recorded per unit weight of dry matter.

From Schultze (321).

Consistent agreement of results

It was seen above (p. 117) that Schultze's results concerning the influence of copper deficiency on catalase were to be a topic of discussion for more than fifteen years and that in 1957 the Wintrobe-Cartwright group recognised their mistake with due honesty. The same is not true, however, of cytochrome oxidase: every author, without exception, arrived at the same result. For example, Gallacher

(*) See p. 111 for Schultze's experiments on the effect of copper deficiency on catalase.

(128), of the Faculty of Medicine of London University, confirmed in 1956 that a *severe* deficiency of copper reduced the cytochrome oxidase activity of the liver to one-twentieth of the normal, and that even a *very slight* deficiency was sufficient to reduce it to a quarter of the normal. This shows how sensitive cytochrome oxidase is to even a very moderate copper deficiency. On the other hand, a very small supplement of copper causes the cytochrome oxidase activity of the liver to increase very rapidly (in less than eight days) to its normal level.

Copper deficiency has a twofold effect on cytochrome oxidase

All the research workers have concluded that the fall in cytochrome oxidase activity of the liver in the presence of a copper deficiency results from the general breakdown of the mechanism for synthesising the hemes that this enzyme contains. Even in 1956 Gallacher (128), who had no knowledge of Green's work published in the same year in the U.S.A., believed that cytochrome oxidase contained no copper.

If, as I believe it is very probable, cytochrome oxidase contains copper as well as hemes, it is more understandable that copper deficiency will reduce cytochrome oxidase activity by means of a double mechanism:

- by disturbing the synthesis of the hemes;
- by directly impoverishing the enzyme with regard to copper.

This double mechanism might explain why this enzyme is so sensitive to even the slightest deficiency of copper.

The functioning of the cytochrome system of the cancerous cell is not normal

As far back as 1938 the Swedish Nobel Prize-winner von Euler (104) was studying the respiratory system of the Jensen sarcoma and found that the cytochrome oxidase had reduced its activity to one-twentieth of the normal. Von Euler concluded: "Defectiveness of the cytochrome system is the main characteristic of the respiratory mechanism of the cancerous cell."

The conclusions reached by this Swedish scientist were largely confirmed during the twenty years that followed. It appeared that there existed, above all, a disequilibrium between the different elements of the cytochrome system in the cancerous cell. In 1954

Greenstein (135, pp. 444-445), an eminent specialist in the biochemistry of cancer, concluded:

"Cancerous tissues, as compared with normal tissues, are characterised not only by a very low content of cytochrome c, but also by a marked disequilibrium in the relationship between cytochrome oxidase and cytochrome c."

Copper deficiency reduces synthesis of the phospholipids (*) in the liver

Gallacher (128) found, in 1956, that even moderate deficiency of copper considerably reduces the formation of phospholipids in the liver of rats. These play a fundamental part in the connection (**) between respiration and energy.

As was seen above (p. 167), Warburg (399) believed that one of the phenomena compelling the cell to adopt the cancerous "way of life" in order to survive is the uncoupling of respiration and energy. It seems very probable, therefore, that a deficiency of copper, by upsetting the synthesis of the phospholipids, runs the risk of throwing out of gear one of the fundamental mechanisms for transmission of respiratory energy, thus forcing the cell to become cancerous in order not to succumb. It will be seen later, moreover (p. 195), that the combined use of copper and a phospholipid (lecithin) has appeared to give good results in the treatment of skin tumours (epithelioma).

Copper deficiency in the soil upsets the metabolism of the sulphhydryl groups in animal cells

In the case of sheep at grass, copper deficiency in the *soil* upsets the metabolism of the sulphhydryl groups (-SH) in the cells of the wool, causing a serious defect in the latter (see pp. 29-30). These sulphhydryl groups are of enormous importance for the respiratory mechanism of the cell and in the transmission of respiratory energy. Disturbance of these groups due to copper deficiency in the soil (and in the diet) therefore risks disturbance of the respiration of the cell in a high degree.

(*) The phospholipids (phosphatids) represent lipids (fatty substances) which are esters of phosphoric acid containing one or two molecules of fatty acids, alcohol and a nitrogenous base. The best known are lecithin and cephalin.

(**) Connection achieved by what is known as oxidative phosphorylation.

Benzpyrene exercises its carcinogenic effect by blocking the sulphhydryl groups

On the other hand, many investigations (60,117) have assumed that certain substances, particularly benzpyrene, are carcinogenic in their action because they inhibit the sulphhydryl groups of certain enzymes: in other words, they upset the metabolism of the sulphhydryl groups in exactly the same way as copper deficiency in the soil.

In 1953 Wood (414) found that intravenous injections of benzpyrene in aqueous, colloidal dispersion greatly reduced the sulphhydryl group content of the blood serum. In 1955 Rondoni (304, p. 191) concluded a long series of experiments on the question of sulphhydryl groups and cancer by saying:

"We must assume as highly probable the development of an interaction between the carcinogenic hydrocarbons and the (-SH) groups of certain protein fractions. It is equally probable that such an interaction plays some part, ill-defined as yet, in carcinogenesis, at least in the case of the hydrocarbons and related substances."

Action of azo dyes on the sulphhydryl groups

The German Nobel Prize-winner Richard Kuhn (196), of the University of Heidelberg, held that azo dyes had a carcinogenic action because, after metabolic transformation, they arrived in the affected cells in the form of quinones obstructing one or more sulphhydryl groups of the enzymes of the respiratory system of the cell.

The blood serum of the cancer patient is impoverished in sulphhydryl groups

In addition, the blood serum of a person suffering from a cancerous tumour contains less of the sulphhydryl groups than normal serum (135, pp. 554—555). This phenomenon indeed is so characteristic that Stricks (358), in 1953, suggested quantitative determination of the sulphhydryl groups in the serum for diagnosis of cancer.

CHAPTER 47

Nutrition affords powerful protection against carcinogenic effects

Discovery in Japan of the carcinogenic action of azo dyes

IN 1932 in Japan Yoshida discovered that an azo dye in the ration fed to rats gave rise to hepatomae (cancerous tumour of the liver). This was the first time that a simple and clearly defined chemical substance had been discovered which, when introduced into the diet, caused cancer.

Immediate attempts ensued in Europe and America to reproduce this Japanese result, but these were a complete failure. At first it was supposed that the Japanese scientist had committed an experimental error. But, as the results were repeated many times over in Japan during the period when the failures were being repeated elsewhere, it had to be assumed that there was a difference in some factor between the Japanese and European experiments which was giving rise to the contradictory results.

Protection afforded by wheat against the carcinogenic action of azo dyes

In consequence, it was said that this discovery of the carcinogenic action of azo dyes could be made only in Japan. In fact, the experimental rats in that country were fed on decorticated, and very often even on polished, rice, while the rats in Europe and the U.S.A. received a basic ration of wheat grains. Finally, in 1940 the Japanese workers (13) came to the following conclusions:

- (1) Development of liver cancer due to azo dyes *depends on the nature of the ration*, particularly on the nature of the cereal and what treatment it has undergone.
- (2) *Whole* wheat has a remarkable capacity for inhibiting the carcinogenic action of azo dyes on the liver.
- (3) *Non-polished* rice has only a moderate inhibiting power. This becomes almost non-existent in the case of polished rice.

It was to appear subsequently that one of the principal "protective factors" contained in the wheat grain was represented by vitamins of the B group, particularly vitamin B₁ or riboflavin.

A crazy story not exclusively Chinese

It is a well-known fact that polishing of rice, by depriving it of its vitamin B₁(*) is the cause of beri-beri. Today every bag of rice has imitation grains containing vitamin B₁ added, with consequent diminution of this scourge in the Far East. Polishing rice with improved machinery is therefore one aspect of the progress of modern science incurring the obligation to add some (only a minute part!) of what has been removed. Is the reader acquainted with the story of the fool who emptied his bucket every time it was full just to have the pleasure of re-filling it?

If only this was merely a Chinese tale! Unfortunately *white* bread is the Western counterpart of the *polished* rice of the Orient. It is enough to recall that white flour has lost a large part of the vitamins B₁ (thiamine) and B₂ (riboflavin) contained in the *whole* grains of wheat (**) (see Table 20, p. 53).

The carcinogenic effect of benzpyrene on the skin is a function of nutrition

It is interesting to go back to some experiments that have sunk into oblivion, carried out some twenty years ago by Maisin (218, 219, 220), the present Director of the Cancer Institute in Louvain (Belgium). These were concerned with the protective role of nutrition against an *external* carcinogenic substance, namely benzpyrene.

The skin of rats was painted with the chemical, giving rise to epithelioma. (***) Injections of benzpyrene were also administered, and these produced sarcoma.(****) Maisin established that the nature of the diet, and particularly the way in which the constituents thereof had been treated, caused the percentage of animals attacked by cancers due to benzpyrene to vary considerably, sometimes *in the proportion of one to two*. From this the Belgian worker concluded in 1941 (220, p. 354):

(*) Also known as thiamine or aneurine (see Chapter 4, pp. 16-18).

(**) In certain countries legislation demands the addition of vitamin B₁ to white flour (170, p. 135). The bucket that was emptied is thus partially (!) re-filled.

(***) Epithelioma = tumour of the epithelium, for example, of the skin.

(****) Sarcoma = tumour of the connective tissue.

Nutrition affords powerful protection against carcinogenic effects 185

"In certain vegetables and foodstuffs there are one or more anti-carcinogenic (*) factors, which are active in the prophylaxis of cancers caused by azo dyes and hydrocarbons.(**)"

Carcinogenic effects of tobacco can be reduced by a suitable diet

Maisin's conclusions are even more topical today, now that it has been discovered that benzpyrene is the carcinogenic substance contained in tobacco tar. It is not at all certain that tobacco causes an increasing number of cancers of the respiratory organs because it is more carcinogenic than it used to be. On the contrary, I am inclined to suppose that the more rapid development of cancer among smokers is due to alterations in the present-day diet, which has thus become *less protective*. White bread alone is very probably responsible for the disappearance of several "protective" factors contained in whole bread. Changes in methods of cultivation must likewise play a part in the diminished protection offered by foodstuffs.

Exhortations to give up tobacco smoking are hardly likely to have any more effect than sermons on virtue, and so the hopes of men must be placed on improving the *protective* characteristics of their diet.

Nutrition is the basis of defence methods against cancer

An authoritative opinion can be called upon in support of this conception of the role of nutrition in "*protective medicine*" where cancer is concerned. The great German surgeon Bauer (30, p. 654), a cancer specialist,(***) has stressed the importance of results relating to the protective role of certain factors contained in the diet, such as, for example, riboflavin (or vitamin B₂) (see above, p. 184). He writes:

"The fact that the carcinogenic influence of azo dyes cannot be exerted if the ration contains sufficient riboflavin is a *discovery of fundamental importance for our methods of defence against cancer*. It shows in effect that we will no longer be exposed to the danger of carcinogenic action if we see to it that our diet is not deficient in a fundamental vitamin. No one can believe that this is a unique and exceptional case. On the contrary, this example justifies the conclusion that *the diet, whatever its nature, can favour cancer* if, for a long period of time, it is lacking in certain essential substances."

These words were written ten years ago by one of the greatest authorities on cancer. Unfortunately, they do not seem to have found much echo.

(*) Maisin uses the word antiblastic.

(**) Which occur particularly in tars, and include benzpyrene.

(***) See p. 266 for another citation from Bauer.

asking: "Did we act wisely in giving up the copper pans used in the past?" (*)

CHAPTER 48

*Copper as a protective element against
carcinogenic colouring substances in our
foodstuffs*

**The carcinogenic action of azo dyes is inhibited by the
copper in the ration**

As long ago as 1946 Sharpless (333), at the Henry Ford Hospital (Detroit), observed that the addition of a *copper* supplement to the diet of rats had a marked protective effect against the carcinogenic action of the butter yellow contained in that diet. These initial observations were confirmed in 1953 by Pedrero and Kozilka (279), using an azo dye (*) similar to butter yellow. The addition of copper to the ration greatly reduced the number of hepatoma caused by the dye. Finally, in 1953 at the Faculty of Medicine of Virginia (U.S.A.), Clayton (66) studied the carcinogenic action of different azo dyes using, for rats, basic rations *absolutely devoid* of copper. These rations he supplemented with quantities of copper varying, per rat, from 3.94 to 300 mg. and found that the 300-mg. dose very greatly reduced the percentage of rats affected by tumours of the liver. The appetite of the animals was not impaired by this copper supplement.

**Were we right in giving up the copper pans used by our
grandmothers?**

It would obviously be interesting from the biochemical point of view to know more about the mechanism by which copper inhibits the carcinogenic action of azo dyes. It is to be hoped that this matter will be cleared up in the future, in which case the result will no doubt be great progress in the improvement of the anti-carcinogenic qualities of Man's diet.

Cookery lovers who read these words will naturally feel justified in

**The protective role of the soil against cancer is revealed
through copper**

But interest in this present connection is centred in the fact that a diet deficient in copper favours the action of certain carcinogenic substances. This deficiency may arise from the nature of the soil (see pp. 29-31), methods of farming (see p. 35) or from drinking-water consumed (see p. 253). It seems, therefore, that there is a *very clear relationship between the soil and cancer* through one of the "dusts" contained in that soil, namely, copper. This relationship will become even more evident on examination of the cancer maps of Holland and Wales (Figs. 15 and 16, pp. 225, 257).

(*) It will also be seen that copper can neutralise the urochrome contained in certain drinking-water (p. 255).

(*) 3'-methyl-4-dimethylaminoazobenzene was used.

CHAPTER 49

*Cumulative toxic effects and negative toxicity***What is a toxic substance ?**

I HAVE always found great difficulty in obtaining, or indeed in providing, a precise answer to the question: "What is a toxic substance?" The first reply which springs to mind is: "A toxic substance is a substance which upsets to a more or less serious extent the vital functions of the organism." But this immediately gives rise to a new question: "At what dosage and with what delay will this toxic substance put into effect its visible injurious action?"

The most accurate reply, most consistent with general opinion and at the same time with current practice, would appear to be: "The toxic dose is the dose that makes its effect felt in the organism by *visible* reactions within *not too long* a period of time."

But a new obstacle looms up: that of defining "not too long" a period of time. Arsenic and lead in small doses are toxic only after a very great number of years, perhaps even never if the doses are infinitesimal. In such instances it is a case of slow, cumulative effects which have only very rarely been studied, as, for example, in the case of tradesmen working with lead paints.

The cumulative toxic effects of carcinogenic substances

This idea of slow cumulative toxicity was to become even more tragically obvious with the development of modern, chemical industry: cancer of the bladder among workers in aniline factories is one of the earliest and best-known cases.

What may be described as the "chemicality" of the modern world finds expression in the addition of a large number of chemical products to foodstuffs. It is estimated that a thousand carcinogenic substances of this kind are in common use at the present time in nutrition (102, 103, 143, 325, 428). Very often these are colouring substances, particularly azo dyes, one of the best known of which is butter yellow which is carcinogenic for the liver (see pp. 183-184).

The terms "toxic" and "carcinogenic" are apparently not identical from the legal point of view

How is one to define the *toxicity* of these carcinogenic substances which, in infinitely small doses, manifest their deadly effect only after many years have passed? Heated discussions have raged round "legal" definitions; and the situation has not been made any easier by the commercial interests involved. What is certain, extraordinary as it may seem, is that the words "toxic" and "carcinogenic" do not represent *one and the same idea*. As Hueper (172, p. 560), Chairman of the "Cancer Prevention Committee" of the "International Union against Cancer", writes:

"The toxic properties of a chemical are not necessarily related to its possible carcinogenic properties. . . . This conclusion deserves special emphasis in view of the fact that 2-naphthylamine, one of the various constituents of the molecules of several food dyes, possess a *remarkably low* toxicity, while being, on the other hand, one of *the most* carcinogenic substances known."

In other words, this powerful carcinogenic substance is not toxic; that is really very disturbing.

Necessary protection against the increasing number of carcinogenic chemicals

All these "official" considerations confirm the belief that there must be no delay in bringing into force regulations which will guarantee that various substances regarded as *NON-toxic* and used in foodstuffs are not *highly* carcinogenic.

Every effort must be directed towards anti-carcinogenic, *protective* medicine; in which case it is necessary to define *negative* toxicity.

"Negative" toxicity

Many substances when absorbed in large doses put their toxic action into effect with little delay. This is "*positive*" toxicity. But if the diet is deficient in this same substance the long-term result is physiological disturbances. This is "*negative*" toxicity.

Copper may be cited here among many other elements. If absorbed in large doses it has a "*positive*" toxicity which gives rise to serious poisoning. (*)

Several chapters above (29, 32, 35) were devoted to the study

(*) It is known, for example, that ingestion of excessive amounts of copper leads to haemolysis and jaundice.

of physiological disturbances caused by copper deficiency in the diet and in the soil. But there is another kind of "negative" toxicity which becomes clearly apparent in the study of the carcinogenic action of azo dyes: namely, the lack of one element, whether a vitamin (see p. 183) or copper (see p. 186), *robs the foodstuff of its protective character against a carcinogenic substance*.

Two categories of "negative toxicity"

There are therefore two categories of "negative toxicity":

(1) The *primary* toxic effect resulting from the lack of an element essential to the proper functioning of cell metabolism.

(2) The *secondary* toxic effect due to the fact that the lack of a protective element allows the carcinogenic substance to exercise its injurious action.

The two effects may, moreover, be merged in one: malfunctioning of the cell resulting from the *primary* effect can diminish the powers of that cell to resist the effect of the carcinogenic substance.

Legislation for the maintenance in foodstuffs of protective, anti-carcinogenic factors is essential

It was necessary in my opinion to create this idea of "negative toxicity", a factor too often forgotten and overlooked.

Regulations must be drawn up in the future eliminating from human food carcinogenic substances with slow, cumulative effect. But that is not sufficient: legislation is also essential guaranteeing that foodstuffs have not been *deprived of their protective, anti-carcinogenic effect*. Legislation of this nature has in fact been applied in countries where the addition to white flour of the protective factor vitamin B₁ (170, p. 135), which has largely been destroyed in the course of milling, (*) is obligatory.

It is even necessary to go one step farther. Regulations will also be required to prevent ill-conceived cultural methods from causing a deficiency of anti-carcinogenic protective factors in foodstuffs, or creating in these foodstuffs mineral imbalances which will reduce Man's capacity for resistance to cancer (see pp. 47-56).

Something must now be said, therefore, about the concept of biological quality.

(*) See p. 184.

CHAPTER 50

The concept of biological quality

The appearance of a fruit or vegetable is no indication of its true quality

VAST propaganda campaigns have been undertaken the world over with the aim of improving quality of agricultural products. This generally means that perfection in size and appearance is demanded from a fruit, but not a thought is given to whether this fruit, so beautiful to look at, is deficient in one of the essential vitamins or mineral elements.

Study of quality in agricultural products

At Geisenheim in Germany a "Federal Centre for Research into the Quality of Agricultural Products" (*Bundesanstalt für Qualitätsforschung pflanzlicher Erzeugnisse*) has recently been set up. If only similar Institutes and Research Centres could be established in every country and the quality of an agricultural product judged by standards other than its perfect external appearance or good measurements! The German Research Centre is under the direction of Professor Schuphan, some of whose work has already been dealt with, illustrating the influence of "dead" mineral matter on elements so fundamental to life itself that they bear the name vitamins (see p. 14). A further investigation by this great scientist into the quality of fruits will now be described.

Great variation in the vitamin C content of apples

Schuphan has shown, among other things, that the vitamin C (*) content of apples can vary within wide limits. He quotes (324a) the instance of two varieties, "Ontario" and "Geheimrat Oldenburg",

(*) Vitamin C or ascorbic acid plays an important part in cell oxido-reductions, in the integrity of vascular walls, in the growth and general resistance of the organism. Its deficiency causes scurvy, characterised by anaemia and multiple haemorrhages, especially around the gums.

which, apart from their size, are identical in appearance and colour. It is impossible to distinguish between them, and yet their vitamin C contents differ greatly. In the course of 1260 determinations on "Ontario" apples an average content of 20.6 mg. vitamin C in 100 g. dry matter was established. But 2806 analyses of "Geheimrat Oldenburg" apples gave an average of 3.1 mg. vitamin C per 100 g., that is, a mere seventh of the "Ontario" content.

Two identical apples do not afford the same protection against scurvy

The effects of these two varieties of apple in the feeding of guinea-pigs were compared. No protection against scurvy was provided by a daily ration of 10 g. "Geheimrat Oldenburg" apples, while 2 g. of "Ontario" variety was sufficient to give protection. The two varieties were also compared in the feeding of babies. After three weeks the group receiving the "Ontario" apples was found to have twice as much vitamin C in the blood as the children being fed "Geheimrat Oldenburg" apples.

Negative toxicity and the anti-scurvy vitamin

This shows how inadequate, and at the same time deceptive, the idea of "external" quality is. These two varieties of apple were identical in appearance, and yet one of them had a *negative* toxicity due to the fact that its low vitamin C content deprived it of the greater part of its power to protect against scurvy. (*)

Soil deficiencies receive attention only when they cause economic losses

Questions of deficiency in agricultural products become subjects of interest only when they find expression in a commercial loss. As long as it is only a matter of a lower "biological value" for Man, (**) no one is concerned.

Copper deficiency in the soil of certain market-gardening regions

(*) It should be noted that it is not at all certain that great variations in vitamin C content would not be determined for *one* apple variety grown on *two* different soils. It was in fact seen above (see p. 14) that mineral elements influence the vitamin content of vegetable products.

(**) More attention is paid to animals, for with them financial losses make themselves quickly felt.

has been studied, not because it might be injurious to human health but because it made the skins of the onions too fragile, and they were broken in the course of grading and transport. In New York State, for example (190), onions produced on so-called "*muck*" soils (*) had very thin skins, which deteriorated badly in the course of handling, giving rise to serious financial losses for the producers and trades-people. On studying the question it was found that the cause was a deficiency of copper (**) in the soil, and the defect was quickly remedied by the application of a fertiliser containing copper (111).

The conception of quality must be broadened

"Protective" medicine of the future will demand that soil deficiencies receive attention, even if they give rise to no commercial loss but are merely (***) injurious to human health. The idea of quality must no longer be concerned with external appearance alone, or financial and commercial repercussions. Quality must mean "*biological* quality", that is, quality for Man, the ultimate end of all science. Analyses will be of help only if they relate to the animal and to Man as well as to the soil and to the plant. But I believe that for a long time to come, if not always, human instinct will remain the great judge of the quality of a foodstuff.

Nobility of the animal instinct in Man

On the basis of chemical analyses of very doubtful value (see p. 25), dietitians have wished to impose upon Man a certain pre-determined diet. But Man eats what he likes and enjoys scorning all the rules and regulations forced upon him. Fortunately, the animal instinct is not dead within him: he refuses to eat green fruits which would cause serious intestinal disturbances; he has a marked distaste for bad meat, fish or eggs that would surely poison him if he ate them. Man's taste and smell remain much more certain guides than all the chemical analyses made. Food which repels may be injurious to one's health, but what one likes is very unlikely to cause any harm.

The words of Oscar Wilde, "I can resist anything except temptation", constitute a good principle for the science of nutrition.

The best judges of the "biological value" of a food will for long

(*) Soils very rich in decomposing organic matter collected in a damp place.

(**) This does not necessarily mean that the soil was lacking in copper. There could have been sufficient present, but in a "non-assimilable" form.

(***) This restriction does nothing but raise the status of the demand.

remain not the dietitians and chemists but the gastronomes, one of the most famous of whom, Brillat-Savarin, made this unusual statement with regard to the importance of nutrition to Man:

"The destiny of nations depends on what they eat."

To which I would add:

". . . and on the soil that produces their food."

Copper as a protective and therapeutic factor against cancer

"General mobilisation" of copper against cancer

IT was seen above that in every patient with a cancerous tumour there takes place simultaneously:

- (1) General mobilisation of copper, bringing about an increase in the copper content of the blood (see pp. 129-134).
- (2) Diminution in the catalase content of the liver (see p. 163) and of the cancerous cells (see pp. 169-171).

This necessitates the same question being asked as in the case of infectious diseases (see pp. 125-128).

It is probable that if the patient is deficient in copper (directly or indirectly) he will not be able to mobilise sufficient quantities of copper to defend himself against the progression of the tumour. If one administers copper to an organism impoverished of it to a greater or lesser degree, will this administration, by speeding up catalase synthesis, help the organism to defend itself against the appearance or development of a cancerous tumour?

Copper, an old cancer therapeutic

It is indeed extraordinary that copper is mentioned so frequently in studies on the therapeutics of cancer, without it being possible to understand the true value of these methods. A few such studies will now be referred to, in chronological order.

Copper and lecithin in the treatment of skin cancers

In 1912 at Barmen (Germany) Strauss (357) treated epitheliomas (skin tumours) on the face with a mixture of copper chloride and lecithin. (*) Previous studies had led to the assumption that choline

(*) Lecithin is a phospholipid with choline, a nitrogenous base regarded as a vitamin (p. 181).

salts (an element contained in the molecule of lecithin) would be active against cancerous tumours. Strauss thought it would be interesting to strengthen the action of copper with that of lecithin. (*) He published photographs of three female faces before and after treatment, which seemed to prove the effectiveness of this method.

Injections of colloidal copper inhibit carcinoma in mice

In 1913, at the University of Liverpool (Great Britain), Gelarie (129) first studied the influence of subcutaneous injections of cupro-ammoniacal sulphate on Ehrlich carcinoma *transplanted* in mice. His results were encouraging, but the local inflammation caused by this substance made him turn to subcutaneous, and then intravenous, injections of colloidal copper, (**) as a result of which the tumour softened and began to degenerate markedly. Gelarie concluded that the favourable results he had obtained with *transplanted* carcinoma made it hopeful that analogous results would be obtained with *spontaneous, normal* carcinoma.

At the same time Loeb had got satisfactory results by treating adenocarcinoma in mice with intravenous injections of colloidal copper. In every case, except two, he produced inhibition of the growth of the adenocarcinoma *so long as the injection was given daily*.

Healthy tissues round the tumour are "vitalised" by copper injections

Moullin (259), in 1918, pointed out the favourable influence of colloidal copper on a woman suffering from carcinoma of the breast and a nodule (probably cancerous) on the liver.

In 1930 Nabias (261) communicated to the "French Cancer Association" results which he had obtained with colloidal copper in

(*) It was seen above (p. 181) that phospholipids such as lecithin play an important part in the *coupling of respiration and energy*, and that any damage to this coupling could aid the appearance of cancerous cells. Strauss' experiment would seem to indicate that external application of phospholipids helps to maintain (perhaps re-establish) the normal mechanisms for the transmission of respiratory energy in places where they are partly damaged and are tending to continue to deteriorate.

(**) Colloidal—in the colloidal state, that is to say, in a very advanced state of subdivision of matter, the latter being in a sub-microscopic state.



FIG. 12. Control rat (*on left*) and rat (*on right*) having received daily doses of copper sulphate prior to inoculation of Flexner-Jobling carcinoma.

From Sugiura and Benedict (363).

the form of electro-cuprol in intramuscular injections. In some cases he used it in association with X-rays. (*)

He describes the effects he observed as follows:

"When one follows patients day by day through a course of electro-cuprol treatment, what one sees is very rapid mobilisation of the necrotic area (**) and its expulsion almost *en masse*. A very clear separation takes place between the necrotic and healthy zones: the necrotic zone is eliminated, the healthy takes on the appearance of a normal wound in process of cicatrisation. In the days that follow, final cicatrisation is effected.

"One is therefore forced to the conclusion that, *under the influence of copper injections, true vitalisation of the healthy tissue takes place*, the result of which is a considerable amount of repair activity."

Prior administration of copper protects rats against an inoculated carcinoma

In 1922, at the Memorial Hospital in New York, Sugiura and Benedict (363) studied the influence of thirty-two different mineral salts, administered orally, on the development of Flexner-Jobling carcinoma inoculated into rats. Buccal administration of the salts *preceded* inoculation for seven to fourteen days, so that, in the words of the experimenters themselves, "the salts might be able to exercise their full physiological effect both *before and after* the inoculation of the tissues with the tumour." *But, of all the many salts tried, only COPPER showed itself to be effective.*

The graph contained in Fig. 12 (facing p. 196) shows the effect of absorbing 22.5 mg. copper sulphate. The circles or black dots are proportional to the development of the carcinoma. Sulphate of copper can be seen to have completely arrested or considerably reduced the development of the tumour.

Fig. 13 (facing p. 196) shows the development of the inoculated carcinoma in a control rat (*on the left*) and in a rat that has received 22.5 mg. copper sulphate, administered orally, each day for fourteen days prior to the inoculation (*on the right*). In the latter the carcinoma has hardly developed at all, but the animal's growth has been retarded.

(*) The richer tissues are in catalase the better they resist X-rays (see p. 169); and copper is one of the elements essential to catalase synthesis. One may wonder, therefore, whether these injections of copper did not "vitalise" the tissues round the tumour by increasing their supply of catalase, thus allowing them to resist the X-rays perfectly while the cancerous cells were destroyed.

(**) Area of dead cells.

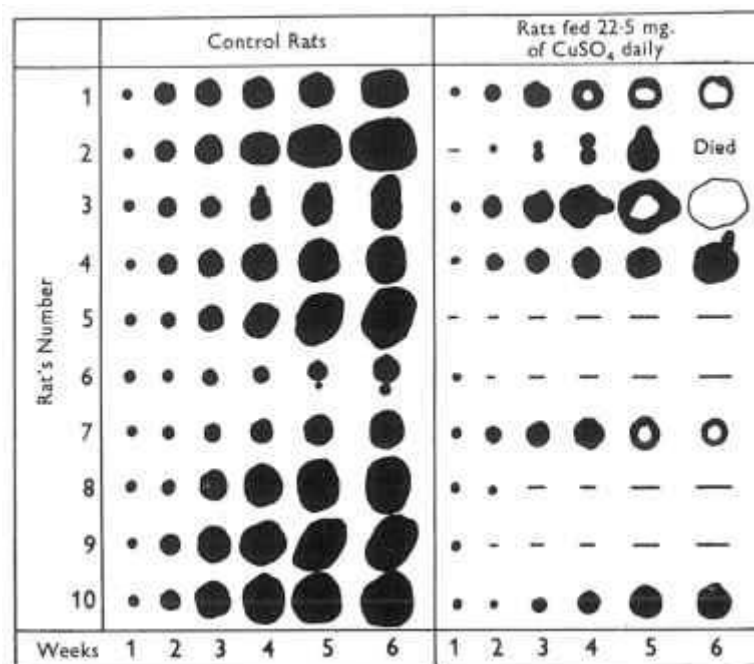


FIG. 13. Daily administration of copper sulphate increases the resistance of rats to inoculation of Flexner-Jobling carcinoma.

(N.B. The black spots indicate the relative size of the carcinoma.)

From Sugiura and Benedict (363).

Catalase, barometer of the regression of a tumour

In all these experiments concerning the therapeutic or protective effects of copper it would obviously have been interesting to know the evolution of the liver catalase, that barometer of regression of cancerous tumours. Unfortunately this was never determined.

It would have been equally interesting, perhaps, to study the combined action of copper and other substances with protective or therapeutic effects, such as the phospholipids, catalase, magnesium salts, iron salts, sulphydryl compounds, etc.

CHAPTER 52

Copper metabolism disorder is one of the causes of cancer

Copper and metabolic disorders in the cancerous cell

WARBURG'S theory of the breakdown of the respiratory mechanisms of the cell as a cause of cancer has been dealt with briefly (see pp. 167-168). In addition, some of the influences exerted by copper deficiency on certain cell respiratory mechanisms were examined (see pp. 178-182).

The result of these studies was the appearance of a very disturbing parallelism between disorders in the metabolism of the cancerous cell (or in the patient with a cancerous tumour), on the one hand, and phenomena caused by a disorder in copper metabolism, on the other.

Relationship between copper and cancer

It seems expedient to review here the various observations made in preceding chapters concerning the relationship between copper and cancer.

(1) (a) Copper is necessary for the synthesis of catalase, the cell's weapon of defence against cancer (see pp. 111, 114).

(b) Every cancerous tumour, whatever its nature, is accompanied by a *profound* disorder of copper metabolism, a disorder expressed in the mobilisation of copper in the blood, whose content of this metal can be more than trebled (see p. 129), in order to speed up the synthesis of catalase, a weapon of defence against cancer (see pp. 169-172).

(2) (a) Copper deficiency reduces the catalase content of the liver (see p. 113).

(b) Every sufferer from a cancerous tumour has less catalase in his liver (see pp. 163, 164).

(3) (a) Copper deficiency upsets the cytochrome system (see p. 181).

(b) The cytochrome system in the cancerous cell is upset (see pp. 180, 181).

(4) (a) Copper deficiency throws out of gear the mechanism of heme synthesis (see pp. 111-113, 115, 116, 125-127).

(b) The mechanism of heme synthesis is out of order in the cancer patient (see pp. 164-166, 168).

(5) (a) Copper deficiency upsets the metabolism of the sulphhydryl groups (see pp. 29, 30, 181).

(b) Metabolism of the sulphhydryl groups is upset in the patient with tumour; and some substances that cause cancer disturb sulphhydryl metabolism in the affected cells (see p. 182).

(6) (a) Copper deficiency disturbs metabolism of the phospholipids (see p. 181).

(b) The phospholipids are elements fundamental to the coupling of respiration and energy. Uncoupling of these forces the cell to adopt the cancerous "way of life" to survive (see pp. 167, 181).

(7) Addition of copper to a ration containing an azo dye diminishes the carcinogenic effect of the latter (see pp. 186, 187).

(8) Copper has often given quite satisfactory results as a protective or therapeutic method against cancer (see pp. 195-198).

Copper metabolism disorder upsets the respiratory mechanisms of the cell

The striking parallelism between these phenomena suggests the following hypothesis: Copper metabolism disorder is one of the causes of breakdown in the respiratory mechanisms of the cell, which, if it is to survive, will be compelled to adopt the cancerous "way of life". Copper metabolism, it is known, can be disturbed by a deficiency (direct or indirect) of copper in the diet or in the *soil*.

One phenomenon is the cause of the other

The objection might well be raised that the parallel phenomena grouped together above are the outcome of one and the same cause: the one is not the result of the other. In my opinion the final argument proving that this parallelism is indeed based on a phenomenon of cause and effect is, as will be seen later (pp. 226, 234), the fact that *cancer is more frequent on soils subject to copper deficiencies*.

Cancer is set in motion by the combined action of several causes

Naturally, it must not be supposed that cancer is started by this *one, single* cause. The important part played by such other mineral elements, as magnesium and zinc, has already been referred to.

A host of causes, both internal and external, contribute towards upsetting the normal respiratory mechanism of the cell and then to the setting up of a new system of respiration (this, moreover, apparently entails two quite separate stages). Nevertheless, it is considered that *a disorder in the metabolism of copper assumes a fundamental role in cancer*.

Disorders of copper metabolism in Man have been very little studied

As has so often been repeated, one of the causes of disturbed copper metabolism, whether in animals or Man, is the diet. A contributory factor in the creation of such a diet is the soil, whether because it is simply low in assimilable copper or because it contains excessive amounts of some of copper's antagonists, molybdenum, zinc, etc. Various factors in the diet can give rise to a metabolic disturbance of this nature: it will be seen later (p. 253) that an impurity, urochrome, contained in what is supposedly drinking-water, and probably in the milk from certain cows, can inhibit within the organism an enzyme with copper.

Up till now people have been content to say that there is no deficiency of copper in Man, (*) and so there is no reason to bother about it. The result is that we are still unaware today of all the copper metabolic disorders that affect Man, although it is twenty years since Heilmeyer and his colleagues proved that not one infectious disease or cancerous state exists that is not accompanied by a change in the copper metabolism of the organism affected.

Here is a vast subject for research, the results of which would certainly throw a great deal of light not only on cancer but also on specific and non-specific defence mechanisms against microbial attacks.

(*) This statement is all the more rash, as no copper "balance" could ever be established.

CHAPTER 53

Vitamin A deficiency is one of the causes of goitre

Despite the therapy of iodine salts goitre remains a scourge of mankind

IN articles, and even in books, on the possible influence of the soil (and the water that springs from it) on Man, it is generally stated that the only known example of such an influence is that exerted by iodine on the thyroid.

Following the discovery of iodine by Courtois in 1812, Coindet (72), in France, as far back as 1820, tested iodine salts empirically as a treatment for goitre. Almost one hundred and forty years have passed since this first attempt, and in that time the treatment has been a definite success in some regions, but not without some serious consequences, such as, for example, Basedow's disease.(*)

In many regions of the globe, however, goitre continues to be a scourge. For evidence of this one need only consult Fig. 16 (p. 257): one sees the importance of goitre in Holland, a country situated near to the sea and where there is no lack of iodine.

Goitre represents a general disturbance of the endocrine system

Due to the close relationship existing between all internal secretory glands, disturbance of the thyroid represents a disequilibrium, of a greater or lesser extent, of the organism. Haubold (149, p. 71) reminds his readers that of patients suffering from goitre, 79 per cent are suffering simultaneously from disturbance of the pituitary, 68 per cent the adrenal glands, 60 per cent the hypothalamus and 52 per cent from liver conditions. Appearance of goitre is therefore the visible and striking expression of a general disturbance within the organism.

(*) Hyperthyroidism: it sometimes occurs in goitre patients following treatment with iodine salts or for other reasons.

Any disturbance in iodine metabolism causes goitre

The popular idea that lack of iodine in the diet (and in the water) is the one and only cause of goitre must be abandoned. The question must be viewed in a more general light: *goitre is a reaction on the part of the thyroid to a disturbance in the metabolism of iodine*. One of the causes may be a lack of iodine in the food or in the water, but the organism can receive adequate quantities of iodine and, for a multitude of reasons, be incapable of utilising this supply normally. It was seen earlier, for example (p. 80), that, of two varieties of white clover, the one that gives rise to goitre in animals is by far the richer in iodine; but that variety also possesses a goitrogenic factor which prevents the thyroid from using the iodine normally.

The main (but perhaps not the sole) function of the thyroid is to manufacture thyroid hormone, the two principal raw materials for which are iodine and the amino-acid known as tyrosine. Scarcity of these raw materials, but also any breakdown in this mechanism of synthesis, brings about a defence reaction on the part of the thyroid which enlarges: this is goitre. Its forms are many and often as different as tuberculosis or pleurisy in the lungs.

In this chapter the influence of vitamin A deficiency on the disturbance of thyroid metabolism will be examined. First of all, however, a few words are necessary regarding the reciprocal action of vitamin A and the thyroid hormone.

Reciprocal actions of vitamin A and thyroxine

The fact that the thyroid influences the metabolism of vitamin A and carotene (provitamin A) hardly seems to be disputed today. This was the conclusion arrived at in 1957 (254, p. 531) by one of the greatest specialists in the subject in his monumental volume on vitamin A. In all his immense work, however, he has devoted only a few lines (254, p. 527) to the question of the influence of vitamin A on the functioning of the thyroid, although he assumes (with many others) that vitamin A can inhibit the action exercised by thyroxine (*) on the basal metabolism.

But if vitamin A exerts an influence over thyroxine it must be assumed that any insufficiency or excess of the former will modify the actions of the latter. The result will be a disequilibrium in the whole

(*) Thyroxine is the iodine substance extracted from the thyroid gland. It has the physiological properties of thyroid extract and seems to be the essential element in the thyroid hormone.

endocrine system.(*) if only by means of modification of the functioning of the pituitary, which will then secrete more or less thyrotropin.(**)

The thyroid with goitre is very low in vitamin A

All the many studies and investigations of the effect of vitamin A deficiency on goitre cannot be dealt with here.

As far back as 1935 Stiner (350), studying in Switzerland the influence of vitamin deficiencies on dental caries in guinea-pigs, established that lack of vitamins regularly brought about the appearance of diffuse parenchymatous goitres.(***) In 1940 Wagner (391) observed that a thyroid gland affected by goitre has a very low content of vitamin A, being but one-tenth of the normal. Adenoma nodules are entirely lacking in vitamin A.

The possible consequences of this vitamin A impoverishment for the tissues of the thyroid will now be examined.

Vitamin A deficiency would cause lesions of the thyroid epithelium

Vitamin A deficiency is known to cause defects in the cornea and in various epithelia, whether of the respiratory tracts, intestine, urinary organs, skin, etc.

The structural unit of the thyroid is represented by the follicle.(****) It is a cavity, round or oval in shape, *bordered by an epithelium* comprising one single row of cells. Since the first observations made by Mitzkewitsch (247) in 1934, numerous research workers (77, 211) have confirmed that a deficiency of vitamin A causes flattening of the cells of the epithelium accompanied by degeneration of the thyroid and swelling of the follicles.

(*) The whole group of internal secretory glands. For this disequilibrium see pp. 107-110.

(**) A thyroid-stimulating hormone secreted by the anterior lobe of the pituitary. This secretion is a function of the quantities of thyroxine present in the blood (see p. 108).

(***) Goitre with inflammations of the epithelium of the thyroid follicles. The word "diffuse" indicates that the hypertrophy affects the two lobes and the isthmus more or less homogeneously.

(****) Also called *acinus* or glandular vesicle.

Synthesis of thyroid hormone is said to take place in the epithelium of the follicles

The Swiss worker Richard (297, 298) has put forward the hypothesis that synthesis of thyroid hormone takes place, at least partly, in the epithelial cells of the follicles. It is conceivable, therefore, that vitamin A deficiency, due to the fact that it causes degeneration of these cells, will disturb to a more or less marked degree synthesis of the thyroid hormone.

The anterior pituitary may also be affected by a scarcity of vitamin A

It may likewise be assumed, as Haubold has done (150, p. 202), that vitamin A deficiency also acts indirectly on the thyroid because it disturbs the functioning of the anterior pituitary and in consequence the secretion of thyrotropin, which regulates the activity of the thyroid.

At the Faculty of Science in Toulouse (France) and in the Museum of Natural History in Paris, Serfaty and Olivereau (273, 331), in 1955, studied the influence of vitamin A deficiency on the pituitary in the male white rat, and found that while the deficiency slowed down thyroid activity, it gave rise at the same time to important histological changes in the pituitary.(*) It would appear, therefore, that vitamin A deficiency has a marked influence on the pituitary, whether direct or indirect.

Two diseases simultaneously in a French Royal Regiment

Today it is a well-known fact that lack of vitamin A causes hemeralopia, or night-blindness: that is, considerable impairment of sight when light diminishes. Work done by a French Army doctor almost two hundred years ago is the first revelation of the connection between goitre and hemeralopia.

A regiment of the Royal Guards was transferred in 1783 from Normandy to Lorraine, where the troops were stationed in the St. Catherine Barracks in Nancy (337). Between 1784 and 1789 a large number of men were affected by hemeralopia, but an Army doctor, Valentin, noticed that those affected also suffered from goitre. He concluded, therefore, that the two phenomena were closely linked,

(*) In particular, they noted a progressive diminution in the beta-cyanophilic cells, which appear to be the producers of thyrotropin, which stimulates thyroid activity.

and entitled his thesis on the subject (379) "Dissertation on Goitre and Hemeralopia". In this work he stresses a particularly interesting fact. The civilians who used the same drinking-water as the soldiers were never affected by goitre, indicating that it was not the water that was responsible, or at least, that it alone could not cause goitre.

Deficiency of vitamin A causes goitre and night blindness

Dr. Rhein (296) of Strasbourg, in drawing attention to this comment of Valentine's, observes that it was quite probably not a mere coincidence and that the same cause, namely a deficiency of vitamin A, was almost certainly responsible for setting the two phenomena in motion. He does not exclude the possibility that vitamin A could have been the direct cause of the hemeralopia, but simply "sensitising" the thyroid to some other goitrogenic factor.

This question will be considered again in dealing with the urochrome (colouring matter of urine) contained in water (see p. 251).

Having examined briefly the various influences which vitamin A deficiency may exert on goitre, the reader is now in a better position to understand how *grass* quality can directly, and in striking manner, influence human health.

CHAPTER 54

Widespread goitre in Europe after World War II

All regions and social classes affected by goitre

IN the years of privation and shortages which followed World War II, a serious wave of goitre inundated Germany and Austria. It developed not only in the classical, endemic goitre regions but also in many areas where it had never been seen before. In Saxony, for example, where the disease was practically unknown, three-quarters of the native and four-fifths of the refugee child population were affected. In regions of Southern Germany where goitre was endemic without being highly developed, nodular goitre (*knotige Struma*) assumed formidable proportions. In Allgäu, Upper Bavaria and the Austrian Alps, hyperthyroidism developed although the endemic form in these regions was hypothyroidism.(*). This means then that in regions where goitre was endemic, not only was there a considerable increase in the number of cases, but there was also a *shift* in the type of goitre.

It should be noted that the children of American Army personnel were not affected.

No question of iodine deficiency in the diet

It was immediately evident that it was not a case of lack of iodine, for 40 per cent of the schoolchildren in Lübeck, for example, a town standing by the sea, were affected. Iodine therapy, apart from exceptional cases, was of little avail.

As was stressed in the preceding chapter, abundance of iodine in the food (and water) does not guarantee normal iodine metabolism in the thyroid.

(*) Hyperthyroidism is characterised by increased thyroid secretions: it also has some of the symptoms of Basedow's disease. Hypothyroidism is an insufficiency of thyroid secretion: vague forms of myxoedema are sometimes observed. (See footnote

Goitre can be due equally well to either form of irregular thyroid activity.

It was a qualitative deficiency, not an insufficiency of food

There was a tendency first of all to think that this goitre wave was due to insufficient food, that is, to a *quantitative* deficiency. But this hypothesis had to be abandoned when it was found that the peasant populations affected by goitre in Bavaria or Württemberg were subject to hardly any food rationing at all.

The search therefore began for a *qualitative* deficiency in the nation's diet. This was conducted by Professor Haubold (150).

Milk and white flour, basic foodstuffs of the Bavarian peasant population

Enquiry confirmed a well-known fact: there is relatively little variation in the diet of peasants in the mountain regions. The Bavarian peasants used mainly the milk and butter produced on their own farms; this they consumed with bread or in combination with flour in the form of various cakes and biscuits (*Milch-Mehlspeisen*). The flour in the bread and cakes, especially from 1939 onwards, was almost exclusively *white* flour. Haubold writes (150, p. 120):

"With the introduction of white flour and new processes for its manufacture, a deficiency of mineral and trace elements, (*) as well as of vitamins of the B group and of vitamin E (tocopherol), made its appearance in the diet. These very important elements are present mainly in the germ of cereals which is eliminated in white flour."

Study of the deficiencies produced by a diet of this nature was concentrated on vitamin A. Some of the most interesting aspects of this work will now be described.

Hemeralopia accompanied goitre in this post-war wave

It was in Munich that Haubold (150, p. 3) first observed that, of 377 adults affected by goitre in the course of this "wave", 75 per cent were also affected by hemeralopia. Twenty-two per cent of these were found to be completely blind at night, even in the moonlight.

During his vast research on cancer in France Haubold (148) came upon Simonin's book (337) in the National Library in Paris, where Valentin's thesis is mentioned. The German scientist compared Valentin's observations with his own statistics, and then tried to determine the causes of a vitamin A deficiency among the Bavarian peasant population.

(*) See Table 32 (p. 209).

Butter, fresh or melted, the main source of vitamin A for certain Bavarian peasant peoples

The main, if not the only, source of vitamin A in the Bavarian peasant diet was their milk and butter. In winter they eat the butter *melted*, a procedure which has the merit of almost completely preserving the vitamin A contained in fresh butter made during the grazing season. Haubold was able to show (Table 32, below) that *the frequency of goitre in the various cantons was clearly a function of the vitamin A content of the butter*.

TABLE 32

The lower the vitamin A content of the butter, the higher the frequency of goitre

Canton or village in the Bavarian Alps	Percentage of children affected by goitre during the winter of 1948	Mean vitamin A content of butter from several farms
Söckering	85	486
Wessobrunn	79	489
Riegsee	32	618
Aidling	13	1015

N.B. Vitamin A contents are given in microgrammes per 100 g. butter.
From Haubold (150, p. 152).

Lack of mineral fertilisers, by reducing the carotene in the grass, aids the development of goitre

The vitamin A content of milk fat is known to be a function of the carotene (*) content of grass. Attempts were made, therefore, to find out what factors had lowered that carotene content. Haubold's figures have been seen earlier in Table 7 (p. 15). They show that lack of mineral fertilisers had contributed greatly to the reduction of carotene in the grass.

Restriction of butter consumption even among rural populations

To this *qualitative* impoverishment of milk and butter as regards vitamin A was added a *quantitative* restriction in their consumption.

(*) Or provitamin A, from which vitamin A is formed.

Requisition of, and the ready market for these products at very favourable prices caused the mountain peasants to reduce to a minimum their own consumption of fresh butter in summer or melted butter in winter.

Thus there came into being the vitamin A deficiency which brought about the development of goitre in these mountain regions.

CHAPTER 55

"On the influence of humidity on mental capacity"

Goitre is twice as frequent in one village as in another near by

IN the course of his investigation of goitre in Upper Bavaria, Haubold (150) noted very curious differences in the frequency of the disease between two neighbouring villages, Aidling and Riegsee, which are barely one mile apart. During the winter of 1948, 32 per cent goitre was observed in Riegsee, compared with 13 per cent in Aidling. Table 32 (p. 209) lists these different percentages and also shows that the Aidling butter contained 65 per cent more vitamin A than that of Riegsee. (*)

The question arising, therefore, was what was the source of this difference in vitamin A content between the two butters; a difference that probably determined the two-and-a-half times higher percentage in Riegsee than in Aidling.

Two neighbouring villages with very different climatic conditions

Let us examine the relative topographical situation of these two villages. The village of Riegsee lies *at the foot of a hill, alongside a lake* that bears its name. The area is often shrouded in mist, and the cold air coming down from the hill creates a relatively cold micro-climate. Aidling lies *above* Riegsee, on the hillside and *facing towards the south*. Fog is rare, sunny days are much more frequent and the temperature at soil level is higher. It is estimated that, in any one year, Aidling has three to six weeks more sunshine than Riegsee.

Herbage analyses carried out in the two villages showed (150, p.

(*) It is not impossible that the drinking-water at Riegsee may have contained more urochrome (see p. 252) than that at Aidling. Water running down a slope increases the risk of pollution to some extent. But Haubold's observations still stand: it must simply be assumed that urochrome action could have been additional to the effect of vitamin A deficiency.

184) *the Aidling grass to contain at least 60 per cent more carotene than that at Riegsee.*

Air mists and goitre development

The following sequence of phenomena thus emerges:

- (1) Mist from the lake has reduced the period of sunshine on the grass.
- (2) Reduction of sunshine (combined with lower temperature) has decreased the carotene content of the grass.
- (3) The lower carotene content of the grass has allowed the cows grazing it (or consuming the hay made therefrom) to produce only milk poor in vitamin A.
- (4) Butter low in vitamin A has caused a higher percentage of goitre among the inhabitants.

Meteorological conditions and the goitre "wave"

Mention was made above of Valentin's work on goitre in a Royal Regiment between 1784 and 1789. It is worth noting that in 1851 Simonin (337, pp. 264, 411), studying the memoirs of the French Army doctor, consulted the *Journal Météorologique* published by Abbe Vaultrin and confirmed that the 1784-89 period in that region had been characterised by very inclement weather and relatively low temperatures. Without being able to explain the reason, Simonin assumed that this prolonged bad weather would have aided the development of goitre.

These observations, inexplicable one hundred years ago, obviously strike one as being particularly worthy of attention in view of Haubold's work at Aidling and Riegsee. The publications of an eighteenth-century French doctor on the subject of goitre show the problem in a light that is at least equally as interesting.

When a great French doctor was ridiculed

The French doctor François Emmanuel Fodéré is known chiefly as the founder of forensic medicine, the subject he taught at Strasbourg University. He was the author of many works, and it is strange that most dictionaries and histories of medicine make no mention of the three books he published on goitre in 1790, 1792 and 1800. The reason may be the apparently frivolous nature of the title of one of them, his last work published in 1800 (121): "Treatise on Goitre and

Cretinism", with the added sub-title "Influence of Humid Air on Mental Capacity".

This title appears fantastic in the extreme and more suited to the work of a quack than to that of a doctor. It was greeted, naturally, with jeers and gibes and the lampooners remarked sarcastically that, on the average, there are no more idiots among the inhabitants of London than among those of Rome.

The lot of this scholar, mocked and ridiculed by the High Priests of Science, was only that of so many precursors: the path of pioneers of progress is strewn with thorns and tears. Nevertheless, it was Fodéré who was right.

Goitre is relatively more frequent in the foggiest part of region

What Fodéré wanted to show, and did in fact demonstrate by his observations, was that goitre (and therefore cretinism) is *relatively* more frequent:

- (1) On damp *northern* slopes than on *southern* slopes of the same hill or mountain.
- (2) In deep, *narrow* valleys suffering from frequent fog than in *wide* valleys where the sun can penetrate.
- (3) In *misty areas* along the side of lakes and by the mouths of rivers.

One hundred and fifty years later Fodéré's observations are confirmed

Haubold's work on Riegsee has largely confirmed the ideas of Fodéré, expressed at a time when nothing whatever was known about carotene or vitamin A. Indeed, it was the German scientist who drew attention to Fodéré's work and to the value of his observations: proof of the necessity to unite the efforts of scientists in all countries in the struggle against goitre. And as evidence of the gravity of this disease in certain regions, I would like to recount a personal experience.

Curse of God or of Man ?

In the course of my enquiries into goitre and cancer I found myself at Riegsee with Professor Haubold. One of the eminent local residents had been kind enough to put his books, documents and statistics at our disposal, and we were in his house. When I had finished

noting down all the figures necessary for my purposes he had a bottle of Rhine wine brought in for us. As I drank the health of my host I noticed, above his head, a family photograph in which every person without exception was suffering from goitre. Seeing what I was looking at, the distinguished Bavarian said: "You see it. What a curse of God!"

A curse it most certainly is, but a curse of men who have upset conditions of their existence and close their eyes to the consequences, failing to initiate the remedy.

CHAPTER 56

Goitre and cancer of organs other than the thyroid

N.B. This chapter may be omitted by the non-specialist reader.

Influence of goitre on the frequency of cancer in organs other than the thyroid

ONE of the most obscure and controversial questions among the thousands of obscure questions concerning cancer is that of the influence that goitre can exert on the frequency of cancerous tumours in organs other than the thyroid.

Tumours of the thyroid itself are not involved. In that particular case, as Dr. Boulanger (48), of the Cancer Institute in Lille (France), recalls, it appears as if at least one form of goitre, the nodular, favours the development of thyroid cancer. This is a fact apparently little disputed in general.

Goitre can be caused by completely different disorders of thyroid metabolism

Unfortunately, in speaking of goitre, one is not referring to a single, well-defined disease. For example, goitre can exist in each of the three following instances:

- (1) *Hypothyroidism*: *insufficient* functioning of the thyroid.
- (2) *Euthyroidism*: *normal* functioning of the thyroid.
- (3) *Hyperthyroidism*: *excessive* functioning of the thyroid.

Within these three categories the variants can be numerous. It is enough to mention the two main forms of hyperthyroidism:

Basedow's disease or diffuse toxic goitre;
toxic nodular goitre.

In 1957 Wolff, one of the greatest specialists in the thyroid, could not but acknowledge: "*The oetiology (*) of either form of hyperthyroidism remains a MYSTERY*" (412, p. 522).

In addition the thyroid is intimately connected with the other internal secretory glands, especially the pituitary (see p. 108). It is very often quite difficult to know whether the thyroid reaction expressed in enlargement (hyperplasia) is due to a *primary* action on the thyroid, or is only a *secondary* reaction resulting from a disorder of the pituitary (or another endocrine gland). Haubold's statistics showing the frequency of other disorders of the endocrine system in persons suffering from goitre have already been referred to (p. 202).

Multiple causes of disorders in thyroid functioning

To turn to the causes of goitre, only a few of the many, that have been mentioned in this work: can it be said that disturbance of thyroid metabolism is identical when it is due to one of the following?

- (1) Iodine deficiency in food and water.
- (2) Obstruction by urochrome of the oxidation of iodide to iodine (see p. 253).
- (3) Action of the anti-thyroid factor contained in certain cabbages (see p. 81).
- (4) Deficiency of vitamin A (see pp. 202-206).

As far as the consequences are concerned it is known that:

the first cause (lack of iodine) gives rise to goitre with *hypothyroidism*;
the second cause (vitamin A deficiency) gives rise to goitre with *hyperthyroidism*.

It is quite evident that so long as goitre is spoken of without the exact nature of the disorder of thyroid metabolism being determined, all the statistics on the relationship between goitre and tumours of other organs will be subject to error and can hardly provide reliable information.

A few of these contradictory theories or observations will now be examined briefly.

(*) *Ætiology* = the study of the causation of diseases.

The myxoedema sufferer would not be attacked by cancer

In 1909 an English surgeon Stuart-Low (359) stated that he had never seen cancer in a patient suffering from myxoedema, (*) a disease due to *hypothyroidism*. He reported, on the other hand, having observed in autopsies carried out on cancer patients that the thyroid was abnormal in size: indicative, in his opinion, of abnormally increased secretion of thyroxine, which would aid the development of the tumours observed. The theory was therefore launched that a reduced rate of thyroid activity tended to oppose the development of cancerous tumours, while increased production of thyroid hormone favoured the development of such tumours in various organs.

Contradictory observations made fifty years ago

These observations made by Stuart-Low fifty years ago led to a mass of experiments, the results of which were most often contradictory, some tending to confirm the English surgeon's two hypotheses, while others showed exactly the opposite. This is not surprising, for types of cancer are infinitely more varied even than types of goitre. Only two examples of these contradictory results will be quoted here, concerning the effect of thyroxine on the development of cancer in other organs.

Non-toxic adenoma of the thyroid is almost always accompanied by cancer of another organ

For three types of hyperthyroidism Desai (92), at the Cancer Institute in Liège (Belgium), found the following percentages of patients with cancers *other* than of the thyroid:

	Percentage of cancerous patients
Basedow's disease (hyperthyroidism)	11
Thyroiditis (**)	20
Non-toxic adenoma (***) of the thyroid	70
Toxic adenoma (***) of the thyroid	13
Carcinoma of the thyroid	3

(*) Myxoedema is a disease characterised by swelling, particularly of the face and hands, due to a mucous infiltration of the teguments. It is the result of diminished production of thyroid hormone.

(**) Generic term including all the many forms of inflammation of the thyroid gland.

(***) Adenoma = a tumour which in its growth more or less closely reduplicates glandular acini, tubules or both.

It seems clear, (*) therefore, that, in the cases examined, hyperthyroidism appears to create conditions favourable to the development of cancer in other organs. This action would seem to reach its most extreme with *non-toxic* adenoma. But when this adenoma grows and becomes toxic or cancerous, quite obvious destruction of the thyroid cells probably takes place. The result is a diminution in the degree of hyperthyroidism and, at the same time, a reduced percentage of cancers in other organs.

Thyroxine reduces the frequency of relapses after the removal of breast cancer

Loeser (213) has defended the view that, in the case of breast cancer, thyroxine would appear to reduce the frequency of relapses following surgical removal of the tumour. It would also appear that patients suffering from a cancer of the breast have a more slowly functioning thyroid (101). It is true, in the latter observation, that there was generally metastasis (**) (general cancer in other parts of the body). Be that as it may, Loeser (213) has defended the following point of view: thyroxine plays an important part in the defence of the normal cell by increasing the metabolic destruction of the carcinogenic substance.

The soil, through the thyroid, influences cancer

Many other results, just as contradictory, could be reported on this relationship between the thyroid and cancer. But if all the experimenters and research workers are not agreed on the nature of the relationship, they are unanimous in acknowledging its existence. No one would dispute the fact that the thyroid exerts a definite influence on the appearance and development of cancer in other organs.

Another point on which all are agreed is that the functioning of the thyroid is *controlled*, through food and drinking-water, *by the nature of the soil*. It must be concluded, therefore, that, even if only through

(*) These are the author's own conclusions. Those reached by the Belgian professor are different.

(**) Note that metastasis has often obscured experimental results concerning the relationship between the thyroid and cancer: the cancer of the breast could have been *started up* by *increased* thyroid activity. Consequently a metastasis of this cancer, by destroying the pituitary and thyroid tissues, produces, as a *secondary phenomenon*, a *reduction in the rate* of thyroid activity.

the thyroid gland, the soil exerts an influence on the development of cancer in the various organs. This will be confirmed when the influence of the soil on the development of cancer in human beings in two countries is examined later (see pp. 223 and 231). But before that, thanks to the relationship between thyroid and cancer, a picture of homoeopathy in reverse can be studied.

CHAPTER 57

What protects against cancer does not necessarily cure it

N.B. This chapter may be omitted by the non-specialist reader.

The effective protective method is not necessarily a good therapeutic method for cancer

ANOTHER factor that has obscured results concerning the correlation between thyroid activity and cancer frequency is a phenomenon frequently observed in the experimental study of cancerous tumours. A method affording effective *protection* against cancer can give only absolutely negative results as a cancer *therapeutic*. There may even be a contrary effect: a *protective* method may favour the development of the cancerous tumour AFTER it has made an appearance.

Riboflavin protects against cancer, but favours the development of the tumour after it has appeared

As mentioned above (p. 183), wheat grains offer protection against the carcinogenic effect of butter yellow, an effect which is also exercised by baker's yeast (245, 364). It was found that one of the protective elements contained in both yeast and wheat grains was riboflavin or vitamin B₂, the addition of which to the ration afforded very obvious protection against the carcinogenic action of butter yellow (187, 188).

The idea was immediately conceived of using this vitamin as a therapeutic agent; but not only did riboflavin not cause the tumour to retrogress, in many cases it favoured the latter's *development* (258, 382). This experiment illustrates the fundamental fact that a ration which protects against the action of a carcinogenic substance is not necessarily capable in consequence of destroying, or even retarding, the tumour once it has been set in motion by that substance.

The same phenomenon is encountered in the case of thyroxine.

Thyroxine protects against dibenzanthracene but does not cure the tumour caused by it

If a carcinogenic substance such as dibenzanthracene is injected into a mouse, tumour formation follows. Bather (29) noted that if thyroxine was injected *at the same time*, the formation of the tumour was retarded and might even not take place at all.(*). On the other hand, if the thyroxine was injected *after* the tumour caused by the dibenzanthracene had established, its influence on the evolution of that tumour was *more or less non-existent*.

This specific observation was to be confirmed more generally, although the effects were reversed.

Removal of the thyroid effects protection against a carcinogenic substance but does not cure the tumour it causes

In New Zealand Bielschowsky (42) has studied the influence of thyroid removal (thyroidectomy) on cancers of the liver in rats caused by oral administration of aminofluorene. The conclusion he reached was exactly the opposite of that reached by Bather (**), because diminution of thyroxine production, resulting from *previous* removal of the thyroid, reduced the frequency of tumours of the liver and retarded their appearance.

These two separate experiments are evidence, once again, of the contradictory results obtained concerning the thyroid-cancer relationship.

But there is one fundamental point on which the two experiments agree, as in Bather's experiment: removal of the thyroid did not exercise the same effect whether it took place *before* or *after* the administration of the carcinogenic substance.

Thyroidectomy *before* administration of aminofluorene *protects* against the carcinogenic action of the latter.

(*) Note that this was not a general influence but a special effect of thyroxine at the very point of injection with the carcinogenic substance. It seems, moreover, that in this particular case the protective effect of the thyroxine is due to the fact that it aids the destruction and rapid elimination of the carcinogenic substance by the tissues.

(**) This need not cause surprise because:

different chemicals were used as the carcinogenic substance; in the first experiment it was a case of an injection local in effect, and in the second of buccal administration which is general in effect.

As stressed above, in the first experiment it is a particular thyroxine reaction at the point of injection, whereas in this present experiment it is a matter of thyroxine suppression for all the organs due to the removal of the thyroid.

Thyroidectomy carried out *after* the tumour has appeared has *no effect whatever* on the evolution or gravity of that tumour.

The effects of the thyroid and thyroxine therefore differ according to whether the tumour has already appeared. The "*protective*" effect is exactly the opposite of the "*therapeutic*" effect.

Reversed image of homoeopathy

Homoeopathy is based on the principle of similarity—"Similia similibus curantur" ("Likes are cured by likes")—and concludes that to cure a sick person, *small* doses of the product should be used which, in *large* doses, gives rise to the disease in the healthy individual.

The three experiments just cited above (and there are many others like them) reveal the principle of homoeopathy in reverse in "protective" medicine: *what PROTECTS does not necessarily cure, and what CURES does not necessarily protect.*(*)

(*) This does not, however, contradict the principle of homoeopathy, because the question of doses is not considered here.

CHAPTER 58

Close correlation between the nature of the soil and stomach cancer in Wales

IN 1868 Haviland (151) reported to the Medical Society of London that it was possible that the soil exerts some influence on the frequency of cancer. Examining the relationship between cancer frequency and the geological map of England and Wales, he came to the conclusion that this frequency was greater on "low-lying clay areas liable to seasonal flooding by rivers".

Thirty years after this first communication, in 1899, Haviland concluded that districts with high-cancer mortality coincide with low-lying clay areas, sheltered from the direct influence of prevailing winds, and traversed by large rivers which seasonally flood the surrounding areas. Elevated districts which are the source of these rivers have low cancer mortalities. Chalk countries are remarkably free from cancer. Water partings of catchment basins where hard rocks occur, especially limestone, also have low cancer mortalities. In river basins with high cancer death-rates, locally outcropping chalk areas are characterised by low cancer frequencies. Areas above the flood-line have lower cancer frequencies than areas immediately bordering the rivers.

No explanation can yet be provided. But it seems as probable to-day as it was in Haviland's time, that if we were capable of explaining this relation we would not be far from solving the problem of the causes of cancer. The means might even then become available, if not to cure cancer, at least to protect men against this scourge.

In the light of knowledge acquired in recent years, an attempt will now be made to reply in some little measure to the question asked by Haviland sixty years ago.

Doctors in Normandy and England confirm Haviland's observations

In 1890 doctors in Normandy (20, 56, 294) reported having observed a greater frequency of cancer on certain clay soils. The

statistical and analytical methods available at that time did not allow them to be more precise in their statements.

In another connection in 1902 Brand (50), in England, confirmed Haviland's results and reported that higher cancer mortality rates are encountered in "districts which lie low and are liable to seasonal floodings, and are characterised by alluvium and subsoils of the various clays". He cited the North and East Ridings of Yorkshire, which stand on the Rivers Ouse, Derwent and Humber, and pointed out that the local inhabitants had named the valley of the Derwent "the valley of cancer".

By comparison, cancer is less frequent in high-lying zones,(*) where there is no flooding and which are "characterised by porous subsoil and the oldest palaeozoic rocks,(**) especially the limestones".

Stomach cancer in North Wales

Recent statistics have confirmed Haviland's observation of the frequency of cancer in certain parts of North Wales, with the additional detail that the relationship is particularly evident in the case of stomach cancer. In 1951 and 1952 Legon (203, 204), of the Geographical Service in London, resumed study of the subject using modern statistical methods and prepared the map contained in Fig. 14 (p. 225), which shows the accumulation of stomach cancer in North Wales.

High content of undecomposed organic matter in the soil favours cancer

The soil in the vegetable gardens(***) of people dying from stomach cancer was studied, particularly if they had lived in the same house for twenty to thirty years. The organic matter content of such soil was measured by ignition.(****) Fig. 15 (p. 225) shows very clearly that mortality from stomach cancer increases as the organic matter content of the soil in the vegetable garden rises.

This study has been pursued in recent years by the British Empire Cancer Campaign, which has carried out many soil analyses in the

(*) See pp. 173, 174.

(**) Palaeozoic era is the geological period of the most ancient fossils.

(***) This method of analysis and statistics might be called a study of the "geological conditions of the habitat". Griffith (140) and Davies (84) have pointed out the difficulties militating against a statistical survey of cancer by regions.

(****) Loss of a soil on ignition can be due to humidity and to calcium carbonate as well as to organic substances. The soil was first dried to 105° C. and then adjustment made (if necessary) on the basis of its content of calcium carbonate.

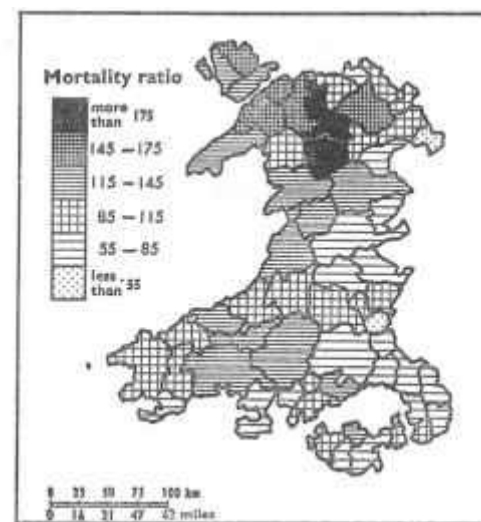


FIG. 14. Frequency of stomach cancer in Wales.

From Legon (204).

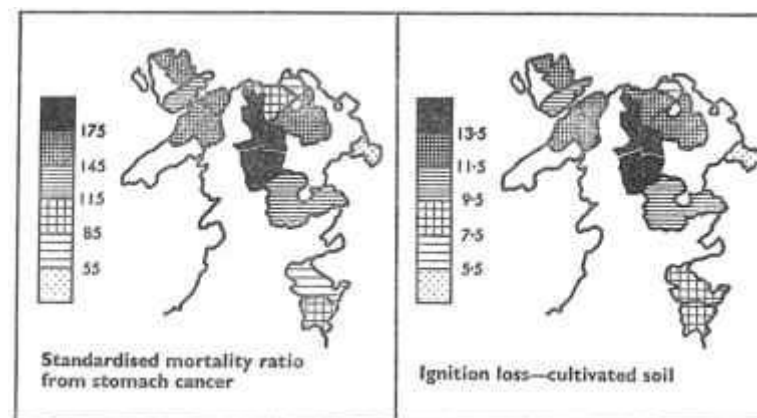


FIG. 15. Correlation between frequency of stomach cancer and ignition loss of cultivated soil.

From Legon (204).

areas of North Wales where stomach cancer is frequent. A marked relationship was also noted between stomach-cancer frequency and loss on ignition of the soil, but more precise measurements in 1955 made possible the observation (354) that maximum frequency of stomach cancer occurred not for a maximum, but for an *optimum*, loss on ignition, this optimum varying with the nature of the soil: the loss on ignition most favourable to stomach cancer was 10-13 per cent for the soils of North Wales and 5-8 per cent for the soils of Cheshire.

Frequency of stomach cancer and organic carbon content of the soil

With the aim of greater simplicity and precision, a relationship was sought between frequency of stomach cancer and the organic carbon content of soils. The result was that, in the case of people who had resided in the same house for twenty years, maximum frequency of stomach cancer was associated with a soil organic carbon content of 25-40 parts per thousand (this being an average content).

The soils of North Wales that favour stomach cancer give rise to copper deficiencies

The soils particularly concerned were peat and badly aerated soils. It is a well-known fact (86) that soils rich in *undecomposed* (*) organic matter, such as peat soils and clays subject to frequent flooding, fix copper in a form non-assimilable for plants,** thus giving rise to various disorders among livestock. *Thanks to grass*, it was seen earlier that in Florida (p. 32) soils of this nature, rich in undecomposed organic matter, caused copper deficiencies among the grazing stock.

Legon thus assumed that it was deficiency (direct or indirect) of copper in the soil that was the cause of the greater frequency of stomach cancer in these areas of North Wales. This point of view was to be confirmed by the study of a soil enzyme.

(*) *Undecomposed* organic matter of peat and other analogous soils is not to be confused with humus. The rate of decomposition of organic matter and of its transformation to humus depends on many factors: aeration of the soil, calcium content, temperature, etc. The more favourable the soil conditions to development of the microflora and microfauna, the more rapid the decomposition.

(**) See the case of the "muck soils" in New York State, which caused copper deficiency in onions (pp. 192, 193).

Soil enzymes

Soil fertility is considered today to be the function of the Lilliputian ploughmen the soil contains (Voisin 388, pp. 40-47). These ploughmen comprise all the microflora and microfauna living in the soil.

Much investigational work has been devoted to the enumeration and determination of these soil micro-organisms, but this has been mainly morphological. It is only in the course of very recent years that consideration has been given to the fact that all the transformations and reactions caused by living things are enzymatic by nature, and that it is more important to know what enzymes and which quantities of them are contained in the soil than to assess the number of micro-organisms, which gives no indication at all of their activity. (*)

Increased invertase content of soils favouring stomach cancer

In the recent enquiry into cancer in North Wales it was decided to study various enzymes contained in the soils thought to be favourable to cancer, in the hope of acquiring more knowledge regarding their biological activity. Invertase (**) was studied in particular and an "index of activity" defined for it. It appeared that the soils on which stomach cancer was most frequently recorded had a very high invertase activity (354). As in the case of organic matter and organic carbon content, however, it was not the soils with the highest figures that produced the greatest frequency of stomach cancer. This form of cancer was found to be most common on soils with an invertase activity index of 15—29. (***)

Transformation of the cupric salts of the soil into non-assimilable cuprous salts

How does this relatively high invertase activity of the soil aid the development of stomach cancer? These studies are very recent (1955-57), and the British investigators have not yet been able to answer this question. My own hypothesis is as follows: invertase

(*) The most important studies on this subject are those undertaken in very recent years at Weihenstephan (Munich) by the Hoffmann group (165, 166).

(**) Invertase or saccharase dissociates saccharose (ordinary sugar) into its two components, glucose and fructose.

(***) The activity index of invertase can reach higher numbers, e.g., more than 60, but such soils are relatively rare.

has the well-known property of reducing cupric salts to cuprous salts, the latter apparently being non-assimilable by plants.(*)

High zinc content of soils favours stomach cancer

The last report of the British Empire Cancer Campaign (356) in 1957 revealed a new and very important fact. Garden soils where the frequency of stomach cancer is particularly high have a zinc content three times greater than that of neighbouring soils(**) where the frequency of this type of cancer is normal.

Zinc is known to be an antagonist of copper. The excessive zinc content of these "cancer soils" is therefore of the greatest interest.

Some of the known characteristics of soils favouring stomach cancer in North Wales

Knowledge of the nature of the North Wales soils favouring stomach cancer cannot be claimed to have progressed much since 1868, the year when Haviland pointed out the correlation between these soils and cancer. Nevertheless, some of their characteristics can be defined:

1. Heavy or peat soils, badly aerated, rich in *undecomposed* organic matter.(***)
2. Soils of this type are known *to cause* COPPER deficiencies.
3. The zinc content of these soils is relatively very high.
4. Soils giving rise to the greatest frequency of stomach cancer possess, in general, the following three "organic" characteristics—

- (a) loss on ignition of 10-13 per cent;
- (b) organic carbon content of 25-40 parts per thousand;
- (c) invertase "activity index" of 15-29.

(*) Knowledge of assimilable, "fixed" and non-assimilable copper in the soil is absolutely nil. Moreover, the accurate methods required for making such a separation are not yet available (314). It must not be forgotten that copper deficiency can stem from a lack of copper in the soil, but it is equally possible for the soil to contain sufficient copper which, for various reasons, is *non-assimilable*.

(**) 101 parts per million of zinc in "stomach cancer soils" against approximately 30 parts per million in neighbouring soils "with normal stomach cancer".

(***) From the geological standpoint Stocks (356, p. 125) writes:

"Mortality from stomach cancer in England and Wales tends to be high where igneous rock is near to the surface and *low in chalk and limestone areas*, and in the survey region the rates tend to be highest where strata of Cambrian age outcrop."

Scientific ignorance must not prevent progress

In the 1957 report of the British Empire Cancer Campaign Stocks (356, p. 125) concluded:

"In the Welsh districts with high stomach cancer mortality, but not elsewhere, its incidence after 10-19 years of residence is excessive where the garden soil has a high content of organic carbon and is still more excessive after 20 or more years of residence where the soil has a medium organic carbon content. ... No such evidence of association has been found between garden soils and cancer of other organs. Something in the soil yet to be identified seems to be the main factor responsible for the peculiarly high incidence of stomach cancer in parts of North Wales. ..."

Little progress has therefore been made, but two things are known nevertheless:

1. Grass has shown that soils of this type cause copper deficiencies among grazing stock (as in the case in Florida, see p. 32).
2. As stated above (see p. 199), it seems very probable to me that a disturbance in the metabolism of copper is one of the causes of cancer.

It would indeed be interesting to know the condition of the livestock in the region as regards copper,(*) a point on which I have been unable to find information. I believe, however, that whatever the data accumulated in this way, the biological experiment is essential if real progress is to be made.

Efforts have been concentrated on soil analyses to the neglect of biological experiment

In this study of cancer in Wales all efforts have been, and are still being, concentrated on *chemical analysis* of the soil. As regards mineral elements, the thousands of analyses undertaken have been concerned with *total* elements. Such analyses, as already stated (pp. 25-28) can provide only very limited information, and the status of chemical analysis must be raised by relating it to the animal as the subject of a biological experiment.

In my opinion, the cancer question in Wales should be dealt with as follows:

(*) Ruth Allcroft (10) produced a map of Great Britain in 1952 showing the regions where hypocuproses had been established in livestock. The North of Wales is not included, but that does not mean that hypocuprosis does not exist there, for these were sporadic, and not systematic, observations.

Rats (*) should be fed exclusively (or almost exclusively) on the produce of vegetable gardens with "cancer soils".(**) A control group should be fed on the same products, but from normal soil. The copper and catalase contents of the livers (***) of the two groups should then be measured, and this will show whether there is any abnormal reduction of these elements in the first group. One would then be quite certain whether a deficiency of copper is involved.

The question could be pursued even farther and *negative* toxicity studied: an azo dye would be added to the ration, or the skins of each group of rats could be smeared with benzpyrene. The percentage of cancer in the two groups would then be compared.

If it transpired (****) that the group fed on the produce of the "cancer soil" is more sensitive to carcinogenic action, a very small amount of copper could be added to the ration to find out whether, as in analogous cases (see p. 186), the carcinogenic action of azo dye diminishes and returns to equal that observed in the control group.

It would probably be even better to add 5 lb./acre [5 kg./ha.] copper sulphate annually to "cancer soils" and see whether the resulting produce would cease to cause the same reduction in liver catalase and then exert a normal, anti-carcinogenic influence. It would then be known for certain that copper deficiency (direct or indirect) is indeed the cause of this abnormally high frequency of cancer. The necessary practical conclusions could then be drawn to "protect" against this type of stomach cancer.

Having studied stomach cancer in Wales, the relationship between the soil and cancer (whatever its type) in Holland will now be examined.

(*) Or mice, guinea-pigs, etc.

(**) The water drunk by these rats should be the same as is consumed by the cancerous owner of the garden.

(***) Not to mention other possible analyses of any organs of the animals.

(****) As seems probable to me *a priori*, but it is not certain.

CHAPTER 59

The soil controls the frequency of cancer in Holland

Refined statistical methods

THE Dutch workers Tromp and Diehl (94, 373, 376) have devoted their efforts to studying the correlation between soil and cancer in general—not only stomach cancer, as was the case in Britain. They used new and highly original statistical methods in an attempt to eliminate different factors which might distort these very awkward and difficult surveys. These methods cannot be described in detail here. All that will be said is that the figures given concerned inhabitants above fifty years of age and that the unit adopted could be:

either the percentage mortality from cancer per 10,000 or 100,000 inhabitants;
or the percentage of "*plus*" districts,(*) that is, districts, where the percentage mortality from cancer was higher than the average recorded for Holland as a whole.

It should also be noted that regions with an accumulation of "*plus*" districts were termed "*plus*" regions.

Iso-carcinoma maps

Just as on a topographical map points of equal altitude are joined by isohyptic lines,(**) so in this present instance maps were drawn up uniting, by means of a so-called iso-carcinoma line, points showing the same cancer mortality figures.(***). At the top of Fig. 16 (p. 257) is the first attempt at an iso-carcinoma map of

(*) The districts were defined artificially according to a certain distance from a central point.

(**) Of course, as Tromp observed (313) contrary to topographical maps, no *proportional* change in cancer mortality between two isocarcinoma lines is recorded on these maps.

(***) It being understood that only inhabitants over fifty years of age are concerned.

Holland. The high concentration of "plus" regions, that is regions of high cancer mortality, in the islands and coastal areas is immediately obvious.

Nature of the soils favouring cancer

What kind of soils were involved? The soils were divided up into many classes and finally grouped together in sixteen categories. The cancer (*) mortality was studied either in decades from 1900 onwards, or for the whole period 1900-40. Table 33, below, shows the

TABLE 33

Classification of sixteen types of soil according to the number of deaths from cancer observed (in Holland)

No.	Name of soil	Total number of carcinoma deaths
1	Beachbank soils	688
2	Loamy river soil	664
3	Reclaimed peat soils	662
4	Permanent moist sandy soils	661
5	Young beach sands	658
6	Peat soils	657
7	Sea-clay soils	652
8	Dry sandy soils (part of year moist)	635
9	Dune sands	617
10	River-clay soils	605
11	Cover sand soils	603
12	Sand on peat	585
13	River sand soils	578
14	Inland dune sand	505
15	Loess and other soil rich in lime	485
16	Brook soils	455

N.B. Total number of carcinoma deaths is calculated per year per 100,000 inhabitants above fifty years of age in the period between 1900 and 1940.

From Tromp (373).

percentage mortality from cancer (of all kinds) on different soils during the period 1900-40.

Among the categories that obviously favour cancer are heavy soils of the type found in Wales. On *sandy* soils, cancer mortality is generally low.(**)

(*) Tromp and Diehl use both words carcinoma and cancer without making any clear distinction between them.

(**) With the exception of certain categories (Nos. 4, 5 and 8).

Cancer is most frequent on soils causing copper deficiencies

It should be remembered that peat or clay soils rich in undecomposed organic matter *cause copper deficiencies* (see pp. 32-34), while such deficiencies are rather rare on sandy soils (see p. 141), as shown by grass (180).

Frequency of cancer mortality as a function of the nature of the soil follows the same order whatever the decade

The soils were finally grouped in seven categories. Table 34, below, shows cancer mortality and also the percentage of "plus" districts on these soils either for different decades or for whole periods. It is noteworthy that, but for one anomaly for the 1930-40 decade, all the groupings, without exception, *are the same*, whatever the period or statistical method.

TABLE 34

Variations in cancer mortality and in the percentage of "plus" districts during the four decades from 1900 to 1940, according to the geological type of the soil

Name of soil	Total number of deaths from cancer per annum per 100,000 inhabitants above fifty years of age in the period						Percentage of "plus" districts for the decade			
	1900-10	1910-20	1920-30	1930-40	Average 1900-30	Average 1900-40	1900-10	1910-20	1920-30	1930-40
Reclaimed peat soils	658	706	661	689	675	678	82	82	55	82
Peat soils	605	667	667	688	667	657	63	60	53	57
Sea-clay soils	595	654	667	693	630	652	56	54	50	58
Sandy soils	562	622	653	651	612	622	48	49	50	55
Cover sand soils	544	611	653	603	603	603	43	47	50	49
River-clay soils	551	603	635	631	596	605	43.5	40	46	41
Loess and other soils rich in CaCO ₃	350	479	578	533	469	435	—	—	—	—

N.B. (1) Cf. Table 33, p. 232.

(2) For the definition of "plus" districts see p. 231.

From Tromp (373).

Since the Welsh investigations had revealed an influence by the soil on stomach cancer, Tromp (376) also studied the frequency of stomach cancer mortality for the seven categories of soil. The order of grouping of the soils in this case was exactly the same as for cancer in general. This is all the more interesting, as the British workers could not show the correlation with any type of cancer other than stomach. It must be remembered, however, that the British analytical

and statistical methods were more limited: they were dealing only with *vegetable-garden soils* and with cancer mortality among the owners of these gardens only. The Dutch studies, on the other hand, were concerned with all inhabitants and all soils.

Striking correlation between soil and cancer in Holland

The regularity of this correlation between nature of the soil and frequency of cancer mortality, whatever the decade or region, is extraordinary. The Dutch workers showed that it cannot be explained by the character of the communities (rural or urban), the different numbers of inhabitants in these communities, or by the non-identical distribution of age of the inhabitants. At the Fifth Congress of the International Society of Pathological Geography in 1954, Tromp (374) concluded:

"The result is so striking that it is difficult to think that it is a mere coincidence, especially when one remembers that many factors can contribute towards camouflaging the results. It seems justified, therefore, to conclude that *the soil exerts a certain influence on the frequency of cancer*, the more so as mathematical study of these results has confirmed that they are significant."

The cancer soils of Holland and Wales are the same: those that cause copper deficiencies

The debatable point about all these statistics on cancer mortality is their basis, namely death certificates, the truthfulness and exactitude of which may vary greatly. Tromp has frequently emphasised the usefulness of strictly secret death certificates as issued in Holland.

Movements of the population are certainly a factor which may seriously upset statistics. But the Dutch worker remarks that he was surprised to find that, except in the very large towns, the population is much more stable than might be expected.

To me, the remarkable fact is that in Holland and in Wales it is exactly the same types of soil that favour cancer: namely heavy soils, badly aerated and rich in undecomposed organic matter, which, as is known from GRASS, *give rise to copper deficiencies*.

As the writer of the editorial in the British medical review, *The Lancet* (16), observed:

". . . there still must be many inaccuracies in death certification . . . the strongest argument in favour of a soil-cancer relationship is its demonstration in two communities as widely separated as Anglesey (Wales) and Holland."

CHAPTER 60

Cancer is less frequent on calcareous areas of different types of soil

Classification of clay soils in Holland according to their content of calcium carbonate

As stated earlier (p. 223), Haviland and other writers had pointed out that cancer is less frequent on limestone soils. Sixty years later the studies carried out by Tromp and Diehl in Holland were to confirm this point of view on the basis of accurate statistics. Clays were divided into four categories according to their origin and content of calcium carbonate (CaCO_3):

1. Calcareous sea-clay soils.
2. *Non*-calcareous sea-clay soils.
3. Calcareous river-clay soils.
4. *Non*-calcareous river-clay soils.

Cancer is less frequent on calcareous than on non-calcareous areas

Table 35 (p. 236) shows:

1. Mortality figures for cancer.
2. Percentage of "plus" districts (*) for the four categories of clay soils defined above—

- (a) during the four decades that had passed since 1900;
- (b) between 1900 and 1929;
- (c) between 1900 and 1939.

Cancer mortality figures or the percentage of "plus" districts can be seen to be always, for sufficiently long periods of time (1900-30 and 1900-40), lower on *calcareous* than on the corresponding *non-calcareous* clay.

This retarding effect of abundant limestone on the development of cancer is confirmed by the fact that mortality from cancer is lowest,

(*) For their definition, see p. 231.

if not indeed one of the lowest, on calcareous loess soils (*) (Tables 33 and 34, pp. 232 and 233).

TABLE 35

Comparison of cancer mortality figures for calcareous and non-calcareous clay soils

	Sea-clays		River-clays	
	Calcareous	Non-calcareous	Calcareous	Non-calcareous
Number of districts studied	130	100	126	38
Cancer death-rates per annum per 100,000 inhabitants above fifty years of age during the period:				
1900-9	580	599	541	588
1910-19	643	665	579	648
1920-29	631	695	627	624
1930-39	690	677	642	650
1900-29	618	653	578	619
1900-39	636	659	597	627
Percentage of "plus" districts for the period:				
1900-9	51	55	41	55
1910-19	49	60	36	45
1920-29	43	59	46	39
1930-39	52	57	41	53

N.B. For the definition of "plus" districts, see p. 231.

From Tromp (373).

Biochemical causes of the unfavourable effect of certain calcareous soils on cancer

Haviland's observation of reduced frequency of cancer in regions with limestone soils has therefore been confirmed by modern statistical methods. He had emphasised that the causes of cancer would become more obvious if the reason for his observation could be explained. Unfortunately, although sixty years have elapsed, his question still cannot be answered. Hypotheses are many, but only three will be dealt with here:

(*) Fine clay without stratification or fossils.

Cancer is less frequent on calcareous areas of soils 237

1. Calcium is known to be antagonistic to zinc and it is not beyond possibility that the latter, if present in too high proportions, may favour the development of cancer (see p. 288).

2. One of Delbet's co-workers, Robinet (302, 303), had noted a low frequency of cancer on certain calcareous soils rich in magnesium (see pp. 54 and 249) such as liassic, (*) triassic (**) or permocarboniferous (***) soils. He was of the opinion that it was the high contents of magnesium in these soils that had an unfavourable influence on cancer development, but the influence might possibly also have been due to the limestone itself. It must, of course, be borne in mind that all calcareous soils are not necessarily rich in magnesium and that all the magnesium present is not assimilable. Unfortunately, the magnesium content of the calcareous clays which were the object of Tromp and Diehl's observations is unknown.

3. The soil, by virtue of the fact that it determines the composition of the water emanating from it, can affect the frequency of cancer through the medium of the drinking-water. It will be seen later (p. 247) that excess silica (SiO_2) in the water appears to favour cancer development, but that this influence can be reduced, or even cancelled, if the water contains sufficient lime (CaO). It is not impossible, therefore, that certain calcareous soils halt the development of cancer by cancelling out to a greater or lesser degree the carcinogenic effect of the silica in the water, or perhaps even in plants.

The equilibrium between calcium and other mineral elements in the soil must be known

Many other hypotheses could be advanced. But it seems as if here again the future will confirm two facts which have frequently been emphasised in the course of this volume:

1. There is probably an optimum content of calcium in the soil at which cancer frequency is lowest: it is not the soils richest in calcium that are least favourable to cancer.

(*) *Lias*. Old word used by English quarriers to describe regular banks of hard limestone. Applies to all the strata at the base of the Jurassic system (secondary formation).

(**) *Trias*. Constitutes the lowest portion of the secondary era. Generally characterised by the grouping of the following three formations: variegated sandstone at the foot, then conchitic limestone (Muschelkalk) and iridescent marls (Keuper).

(***) *Permocarboniferous*. Name under which the Permian formations are often grouped in a single system. These are the upper strata of the primary era, lying on top of the Carboniferous and underneath the Triassic deposits.

2. Calcium content cannot be considered separately without taking the *other* mineral elements into account; it is the mineral *equilibria* and not the individual elements that govern the phenomena of life.

A well-known example is that of certain calcareous soils derived from the lower lias, as, for example, in Somerset (*) (Great Britain) (see p. 41), which are too rich in molybdenum. They cause an indirect deficiency of copper, with consequent severe scouring in cattle, known as teart. The importance of disorders in copper metabolism where cancer is concerned has already been referred to (see p. 199), and it seems probable to me that calcareous soils of this nature (a very special group) should rather tend to favour the development of cancer.

The problem becomes even more complex when the calcium metabolism of the cancerous cell itself is examined.

Calcium and potassium contents of the cancerous cell

As long ago as 1904 Beebe (32a) pointed out that, in all human cancerous tumours, the calcium content *diminished* and the potassium content *increased* in proportion to the malignancy of the tumours. This finding was confirmed by Clowes (67a) in the following year, 1905, on one hundred specimens of Jensen adenocarcinomas in mice.

Since these first results were published the volume of research on the subject has increased greatly; but, as is always the case with cancer studies, the findings have been anything but in agreement. Nevertheless, the majority of the research workers got results very similar to those of Beebe. Shear (334a) reviewed the question in 1933 and was of the opinion that there was sufficient proof available to justify the statement that, in many cells, calcium *diminishes* and potassium *increases*. More recently Sontzeff (364a), in 1944, and Carruthers (61a), in 1946, observed a *considerable diminution* in the calcium content of squamous-cell carcinomas in humans as well as in mice. Brunschwig (56a) and Dunham (99a) confirmed in 1956 that, in Man, tumours of the stomach and colon contained less calcium and more potassium than adjacent normal mucous membrane. De Long (90a) also studied, in 1950, the calcium and potassium contents of the colon in humans, comparing them with the contents of neighbouring mucous membranes. He found that on the average, with

(*) It would obviously be interesting to have comparative statistics of cancer mortality for the "teart" and "non-teart" regions of Somerset. If these exist, I was unable to obtain them.

this type of carcinoma, the calcium content of the cancerous cells was *reduced* by 44 per cent and the potassium content *increased* by 60 per cent.

The observations made by Beebe more than fifty years ago would thus appear to be adequately confirmed.

Low calcium content is characteristic of the cancerous cell

The increased potassium content of the cancerous cell is not, however, completely specific to that cell, for all cells in the course of rapid *proliferation* have a relatively higher potassium content. The tissues of the rat *embryo* contain twice as much potassium as those of the *adult* rat.

De Long (90a), at the University of Pennsylvania, studied the calcium and potassium contents of liver cells in the course of regeneration in the rat: the liver being recognised as an organ whose cells have a great capacity for rapid growth. The calcium contents of such cells were unaltered, but the potassium contents were increased by an average of 11 per cent. This increase is much less than in the cancerous cells of the colon, therefore. De Long, however, considered that the higher potassium content of cancerous cells is (at least in part) an expression of cell multiplication. On the other hand, the American scientist concluded that *the diminution of calcium content is peculiar to the cancerous cell*, since it is not found in rapidly growing cells.

Calcium metabolism in the cancerous cell is no longer normal

It was important to know whether or not this lower calcium content of the cancerous cell was due to a lack of available calcium in the organism. De Long (90a) had observed no significant reduction in the content of available calcium in the blood or body fluids. He thought, therefore, as Lansing (198a) had done previously, that the binding power of cancer cells for calcium is diminished. In other words, the calcium metabolism of the cancerous cell is upset.

The cause of this defect is unfortunately unknown, but at least one of its consequences is recognised. It appears that the greater part of the calcium in a cell is situated on its surface (325a): with the result that, in the cancer cell, the reduced content of calcium brings about an alteration in the surface properties, in particular a reduction in mutual cellular adhesiveness (72a, 237a). In consequence, the invasiveness of the cancerous cell is increased, which may explain

not only its tendency to spread through the tissues but also the phenomena of metastasis. (*)

Haviland's wish still holds good

The importance of these findings, incomplete and imperfect as they may be, is greatly enhanced when they are viewed in the light of the statistics quoted at the beginning of this chapter showing that, for a certain type of soil, cancer is less frequent on the most calcareous portions. Within the present limits of our knowledge it is impossible to see what correlation this defect of the cancer cell may have with a calcium deficiency in the soil. Haviland's words can therefore only be repeated: "If we solved this problem we would probably know the causes of cancer." To which I would add: "We might even be able to master this scourge."

(*) The transfer of disease from a primary focus to a distant one by the conveyance of causal agents or *cells* throughout the blood vessels or lymph channels.

CHAPTER 61

Excessive soil moisture favours cancer

On the same type of soil, cancer mortality increases with soil moisture

As long ago as 1868, Haviland, in London (see p. 223), stated that cancer frequency was higher on *low-lying clay areas liable to seasonal flooding by rivers*. This result has been confirmed by many investigators since, but without the basis of detailed statistics.

The question was taken up by Tromp and Diehl (373), employing the statistical methods referred to above. They established a very clear relationship between the moisture content of a certain *type of soil* and cancer frequency. Their results for sandy soils for the years 1900-39 and for each of the decades within that period are contained in Table 36 (p. 242). Except for one decade, where the figures are almost stationary, cancer mortality increases with the moisture content of this soil type.

Soil moisture and stomach cancer

In France in 1950 Durand (100) pointed out the existence of a correlation between extent of rainfall and frequency of stomach cancer. After long periods of heavy rainfall a marked increase in frequency is observed in the following year, and sometimes even in the following two years.

Excessive moisture prevents the transformation of organic matter to humus

It is not impossible that meteorological conditions may directly influence cancer frequency and that a damp atmosphere favours its development. But until the beginnings of proof are available for a hypothesis of this nature it must be assumed that moisture favours cancer by modifying the physical and chemical characteristics of the soil. It may be supposed, for example, that moisture alters the quantities of undecomposed organic matter present in the soil,

reducing the rate of their transformation to humus. It was seen above (p. 226) that this accumulation of organic matter fixes copper in a form non-assimilable for plants, thus creating a copper deficiency, a possible cause of the development of cancer.

TABLE 36

Influence of the moisture in sandy soils on cancer mortality

Sandy soil	Period				Average 1900-39
	1900-9	1910-19	1920-29	1930-38	
Dry	591	631	633	686	635
Damp	597	642	671	692	650
Very damp	678	626	747	718	692

N.B. The figures indicate the total number of deaths from cancer per annum per 100,000 inhabitants above fifty years of age.

From Tromp (373).

Variations in soil moisture affect the equilibrium of mineral elements in the soil water

Variations in moisture alter the amounts of different mineral salts (*) contained in the interstitial aqueous layers of the soil as well as in the water table. This modification of the mineral composition of soil water ultimately affects not only the mineral but also the organic (pp. 5-24) composition of plants growing on that soil, and in the long run the animals and human beings who consume these plants.

Excessive soil moisture favours an excess of potassium over magnesium

In the course of the symposium organised by the International Potash Institute in 1954, Schuffelen (320), of the Wageningen Research Centre (Holland), recalled that one of the most important mineral antagonisms is between potassium and magnesium, and that numerous experiments show that application of potassium fertilisers may contribute to magnesium deficiency. It has often been found in Holland that deficiencies of magnesium are much more frequent in damp spring seasons.

Table 37 (p. 243) shows how the ratio of potassium to magnesium is *doubled* in a clay soil when the soil moisture rises from 11 to 28 per

(*) To be more exact, anions and cations.

cent.(*). Soil moisture, therefore, will speed up potassium absorption by the plant relative to that of magnesium.

TABLE 37

Influence of moisture in clay soils on the ratio of potassium to magnesium in the soil water

Percentage moisture in soil	Potassium/magnesium ratio
11	0.21
17	0.20
22	0.42
28	0.45

From Schuffelen (320).

The consequences of this potassium/magnesium disequilibrium in the *soil*, and how it helps to create a similar disequilibrium in the *blood* of animals and men, have already been described (pp. 47 and 54). It is also known that too high a potassium/magnesium ratio may probably favour the development of cancer. Schuffelen's paper, therefore, makes it easier to understand how increased soil moisture, by accentuating a possible (indirect) deficiency of magnesium, will aid the development of cancer.

Frequency of cancer is a function of month of birth

I frankly admit that the idea would never have occurred to me to construct a curve for cancer frequency as a function of the month of birth. Statistics of this nature were collected for Vienna (Austria) and for the Soviet Zone of Germany (98) as shown by the curve at the right of Fig. 17 (p. 259). It will be seen that the frequency of cancer is *17 per cent higher among those born in JANUARY than among those born in JULY*.

Many hypotheses could be thought up in explanation of this relatively greater frequency of cancer among people born in winter. It may be supposed that the child *before* birth via the placenta, or *after* birth via its mother's or cow's milk, is deprived of certain elements which are less plentiful in the winter diet: it is a well-known fact, for example, that winter feeding contains less carotene and less vitamin A. The water drunk by the mother may also affect the child;

(*) Result of the so-called Donnan's laws.

and it has just been stated that the mineral equilibrium of water is less favourable in damp months. (*)

It would be interesting to have similar statistics for countries on other latitudes and with different climates, and also to see, for example, whether those born during heavy monsoon rainfall are more subject to cancer.

(*) It would be interesting to know what *seasonal* variations occur in the mineral equilibria of spring water.

CHAPTER 62

Filtered river water, used for drinking, favours the development of cancer

Filtered river water partly replaces water from wells in modern civilisation

ONE of the most serious problems that have always confronted mankind is that of absolutely safe drinking-water. Water from wells is available in limited quantity only, but the population of the world never stops increasing. For this reason purified river water has had to be used.

My wife recently came across the following passage in a French women's magazine (115) which she was quick to bring to my notice:

"Many springs supply Paris with water. But Paris has extended, and its population as well as its industrial requirements have increased. The available spring water having become insufficient, filtering stations have been set up on the banks of the Seine and the Marne. At first these stations were to provide 100,000-200,000 m³ per day. Now 800,000 is demanded of them. The stations have not been enlarged, which means that they are forced to filter more quickly and *less well*."

"The situation is made even more serious by the fact that the water arriving at these stations is more and more polluted by urban, and particularly by industrial effluent. Treatment of it, therefore, becomes ever more difficult."

These observations could be applied to almost all the cities in the world of large or medium size.

The effects of this so-called purified river water on the development of cancer in Man will now be examined.

Purified river water favours cancer in London

In 1947 Stocks (352) noted that deaths due to cancer in London were differently distributed according to areas. These differences could be explained neither by age, social conditions nor hours of exposure to sun.

London gets its water from four different sources: purified water

from three rivers (the Thames, the Lea and the New River) and from wells. Stocks found that districts supplied with water from *wells* had a much lower cancer mortality figure than those supplied with the purified water from the three rivers.

This was a very disturbing observation, since, without purified river water, it is impossible at the present time to ensure supplies of drinking-water for large modern cities. It led Tromp and Diehl, in Holland, to study more closely the influence of drinking-water on cancer: for which purpose they used the statistical methods previously referred to (pp. 231, 232).

Cancer mortality in Holland is higher with purified river water than with water from wells

The aim of the Dutch workers first of all was to determine what relationship might exist between origin of water and cancer mortality. In a preliminary study they divided up water, according to its origin, into four categories which *favour* cancer in the following descending order:

1. Purified river water.
2. Water from heath soils (shallow groundwater).
3. Water from dune zones (shallow groundwater).
4. Water from wells (deep).

TABLE 38

Cancer mortality in Holland relative to the origin of the water

Origin of water	Cancer death-rate per 100,000 inhabitants
Purified river water	606
Water from heath soils (shallow groundwater)	594
Water from dune zones (shallow groundwater)	585
Water from wells (deep)	568

N.B. Cancer mortality refers to inhabitants above fifty years of age.

From Tromp (373).

The highest percentage of "plus" districts (*) was also found in regions supplied with purified river water.

Stock's findings were therefore confirmed: *cancer mortality was higher with purified river water than with well water.* Tromp and

(*) For definition of these see p. 231.

Diehl thought that the carcinogenic effect of the former was probably due to the presence of a certain number of dissolved mineral or organic substances; the source of these being sewage from the large factories. This is the case with the Rhine in Germany and with many other rivers flowing through the Dutch industrial zone.

Study of the mineral composition of water

Tromp and Diehl unfortunately neglected the organic substances contained in purified river water, and never brought up the question of urochrome, (*) for example (p. 252). Instead they studied the possible relationship between the mineral composition of water and mortality due to cancer and tried to relate that composition to the nature of the soil where the water originated.

The analyses carried out by the Dutch Water Services unfortunately allowed them to take only four mineral elements contained in drinking-water into consideration:

lime (CaO);
silica (SiO₂);
magnesium (MgO);
manganese (MnO).(**)

For every type of drinking-water originating from a soil whose nature had been determined, the percentage of "plus" districts (***) was calculated and then, using a special mathematical method which cannot be explained here, that percentage was compared with the water's content of the four mineral elements listed above.

A high silica content in the water favours cancer

A constant and on the whole very obvious result was obtained (375): highest cancer mortality was associated with water relatively rich in silica (****) (Table 39, p. 248).

Tromp, being very cautious, has stressed that it was possible that the silica acted directly on the development of the cancer; but that the high content of silica may also indicate the presence of other mineral elements (not analysed) *which always accompany it* and which would be the real cause of the cancer.

(*) Hettche's publications (1954) are simultaneous with those of Tromp and Diehl that I have to hand (1954, 1955).

(**) These are the only trace element taken into consideration. Copper and molybdenum, for example, were not analysed.

(***) For definition see p. 231.

(****) More than 20 mg. SiO₂ per litre.

Abundance of magnesium in water reduces the frequency of cancer

According to Tromp (375) peat soils and sea-clays, on which the number of deaths from cancer is high, supply water low in magnesium. River clays, on the other hand, on which the number of cancer deaths is relatively low, give water rich in magnesium (Table 39 below).

TABLE 39

Mortality from cancer as a function of the abundance of magnesium in the water

Type of soil	Percentage of districts with a cancer mortality higher than the average for Holland	Mg. magnesium per kg. dry matter in soil	Percentage of districts where the water is richer in than the average for Holland		
			Silica	Magnesium	Manganese
(1) Peat soils	58	375	67	20	20
(2) Sea-clay soils	54	406	66	21	13
(3) Sandy soils	50	45	51	21	19
(4) River-clay soils	42	32	20	59	48

N.B. (1) Magnesium = MgO; silica = SiO₂; manganese = MnO.

(2) Average magnesium content of drinking-water in Holland is 13.6 mg., average silica content 19.8 mg. and average manganese content 0.25 mg./litre.

(3) Cancer mortality figures refer to the period 1900-39.

From Tromp (374, 375).

It is interesting to note that the two types of soil that supply the water with the lowest magnesium content are those which themselves contain the most magnesium—further proof of the limitations of soil analyses, where, almost always, it is only *total elements* that are determined. High acidity and a high content of potassium in soils are sufficient to explain that magnesium, although abundant in the soil, is present only in very small quantity in the water that has "washed" that soil.

The Dutch observations would appear to confirm Delbet's theory

Tromp did not omit to call upon the ideas of Delbet and Robinet (see pp. 54, 237), according to which magnesium deficiency in water and in the soil favours the development of cancer. (*) The Dutch workers believe that their results would tend to confirm Delbet's theory but that more results are required before absolute confirmation can be claimed.

Manganese in water as a protective element against cancer

In the light of his results, however, Tromp (375) was of the opinion that it was abundance not of magnesium, but of *manganese* in the water that would assume the most important "protective" role against cancer (Table 39, p. 248).

Personally, it seems to me that the positive correlation between cancer mortality and the manganese content of the water is less marked than the *positive* correlation with magnesium content and the *negative* correlation with silica content.

But, as these were only preliminary studies, it is difficult to pronounce definite judgement, the more so as elements as important as copper and molybdenum were not analysed.

Cumulative effect on cancer of the same drinking-water consumed over a period of many years

Improbable as it may seem, these studies by Tromp and Diehl are the first (**) to try to establish scientifically a correlation between the composition of water and frequency of mortality from cancer. Their great merit lies in having drawn attention to the considerable danger of cancer development inherent in certain drinking-water. The danger is all the greater because it is a matter of identical *cumulative* effects affecting the organism *over a period of many years*.

The foodstuffs we consume may originate from many different parts: oranges from California, meat from the Argentine, bananas from the West Indies, but we consume the *same* water for years and years on end. Moreover, if this is spring water, a close bond is created with the soil of the water's origin.

It is in the interests of "protective" medicine, therefore, that this

(*) Delbet was content to analyse only *total* magnesium in the soil. As has just been seen, this would often give false results.

(**) At least to my knowledge.

study by Tromp and Diehl should be followed by many others of the same nature.

Necessity of studying the "protective" capacity of drinking-water against cancer

With water, as with all foodstuffs, it is essential to study not only its possible carcinogenic character, but also its *protective capacity* against cancer. It must be fed to rats and guinea-pigs for months or even years. Then it will be possible to study the comparative resistance of these animals to a carcinogenic action, such as the addition of an azo dye to the ration or to the smearing with benz-pyrene.

But it is not only the mineral equilibrium of filtered water that endangers human health. These so-called purified water supplies also contain organic substances, only a proportion of which has been retained by the filtering plants. It is this aspect that will be examined in the following chapter.

So-called drinking-water can upset copper metabolism

Supposedly purified river water may still contain many organic substances

IF the importance of the subject to be dealt with in this chapter is to be fully understood, it must be remembered that the purification to which river water is subjected before being used for drinking purposes does not remove all the organic substances it contains.

Reding, a member of the Belgian Commission for the Study of Cancer, calls to mind the following points:

"Microbial pollution of water has attracted all the attention while hardly any has been paid up to now to *chemical* pollution, less spectacular it is true, but just as serious in the long run. It has been established that drinking water derived from the treatment of river water into which flows the effluent from factories engaged in the refining of mineral oil, has given rise to a certain number of cases of cancer in animals smeared with eluates obtained by filtration on adsorbent carbons."

These are disquieting thoughts, but the cause of pollution, which is about to be studied, is even more disturbing. It is not a case of "abnormal" foreign bodies being contributed by ultra-modern factories. The pollution which will be dealt with here is *normal and common*, and occurs in all water, whether in the country or in the town.

Goitre is frequent in Holland in regions where the water is rich in iodine

Hettche (155), Director of the Institute of Hygiene in Hamburg, published the results of his studies on goitre in Holland in 1954. The map on the lower part of Fig. 16 (p. 257) shows the frequency of goitre in that country. The data show that the iodine content of water in the goitre regions is often higher than that of the water in the regions with no goitre. It seemed improbable too that a simple

deficiency of iodine could be the cause of goitre (*) in a country with a maritime climate and where sea fish is eaten in quantity.

It was quickly noted that the water in the goitre regions was rich in nitrate. This substance in itself does not cause goitre, but its presence indicated that the water was still contaminated with elements from the soil surface. Mention should be made here of the fact that the layers from which the water in question sprang were *not very deep*. The water table in these regions, moreover, was always high.

What was the element in this fairly shallow water that had not been filtered by the soil and had an anti-thyroid influence? This was the problem Hettche set out to solve.

In goitre regions on a hillside, frequency of the disease increases with decreasing altitude

It has been known for a long time that in mountain areas subject to goitre the frequency of the disease increases, the lower the altitude of the village. The reason for this was assumed to be that the water was increasingly polluted by sewage from the villages farther up the slope: this pollution was generally assumed to be *microbial*. Later it was shown that goitre is not an infectious disease.

Urine and liquid manure contain an anti-thyroid factor

Hettche (155, pp. 50-51) tried to establish what the anti-thyroid factor could be that was present in the water in increasing quantities as it flowed down a populated hillside. In the course of experiments with rats the German scientist succeeded in proving that liquid manure contained a goitrogenic factor: a factor which he precipitated with silver nitrate. Subsequently he was able to isolate the same substance in fresh urine (155, p. 71). When the product (isolated from either fresh urine or liquid manure) was fed to rats it was found to possess a strong anti-thyroid capacity which manifested itself in the animals in the following phenomena:

elimination of the colloid; (**)
extensive enlargement of the thyroid;
hyperaemia of the capillaries.(***)

(*) Remember (p. 80) that it is the clover richest in iodine that causes goitre, because it contains a goitrogenic factor which prevents utilisation of the iodine.

(**) Gelatinous substance contained in the follicles of the thyroid.

(***) Increased blood circulation with dilatation of the vessels.

Urochrome, the colouring matter of urine

The conclusion was finally reached that the substance that had been isolated was the colouring matter of urine—urochrome.

As far back as 1798 Fourquoi and Vauquelin in France had tried to isolate the colouring substance in urine. In 1862 Tichborne was successful in precipitating the *copper salt* of this substance; and in 1864 Thudicum gave it the name urochrome. Since that period it can hardly be said that much progress has been made in the study of urochrome. The only two important works on the subject are those by the Pole Dombrowski (96) in 1907 and by Rangier (291, 292) of the Faculty of Medicine in Paris in 1935. Even today the exact composition of urochrome is still unknown.

Urochrome combines with the copper of an enzyme of the thyroid

The point of particular interest is that discovered by Tichborne in 1862 and confirmed frequently since: *urochrome combines with copper*. Hettche was of the opinion that an oxidase with copper oxidised iodide (taken from the blood), to iodine in the thyroid; this iodine subsequently combined with tyrosine to form thyroxine, or thyroid hormone. It is this oxidative stage in the synthesis of the hormone that would be obstructed by the urochrome in drinking-water that had been insufficiently filtered (155, p. 66).

Complete absence of microbes does not guarantee the quality of water

The present Pasteur-dominated mentality is satisfied if methods of filtering and purifying water provide a guarantee that the water is completely devoid of virus and bacteria. It is by no means certain, however, that in that water:

1. The mineral equilibrium is satisfactory (this was dealt with in the preceding chapter).
2. Impurities such as urochrome have all been eliminated.

Opinion of a world authority on nitrate in drinking-water

In a very complete, and also noteworthy, work published by Taylor in 1958 on the subject of drinking-water analysis (370), not a word is said about analysis of the urochrome contained in water.

This in itself is disturbing, but I found other points even more startling.

Hettche stressed that the presence of nitrate in water is parallel to the presence of urochrome because both originate from the same pollution, namely badly filtered excrements which are not removed from the water. This is what is confirmed by Taylor (370, p. 29), who writes:

"Nitrates are present in most waters, but practically their only concern with purity and wholesomeness relates to considerations of pollution by sewage or manure, since they may be derived from the oxidation of nitrogenous organic matter of animal origin."

The English specialist also writes in another connection (pp. 145—146):

"The nitric nitrogen occurring in waters used for domestic purposes varies from 0.0 to 70.0 or more mg. per litre, though few waters are found with either of these extremes. Nitrates are evidence of organic pollution. Deep wells are known to yield waters which are frequently free from nitrates, and the samples of water containing such large amounts as 70 mg. of nitric nitrogen per litre have been from shallow wells."

What is *rapidly* dangerous for babies may be *slowly* dangerous for adults

Since no one disputes the fact that some water may contain nitrate, the question arises as to what are the danger limits for the nitrate content of water. Taylor (370, p. 146) provides the following information:

"Waters from many gravel beds contain 20 or more mg. of nitric nitrogen per litre, doubtless derived from manurial matter, yet such are used for public supplies and are perfectly wholesome except for use in making up artificial feeds for infants, when such water should not be used."

This is an important point: *water containing 20 mg. and more of nitric nitrogen can be consumed by adults, but not by babies*. Indeed, when this water was used (74) to dilute concentrated or powdered milk for babies the infants were affected by cyanosis (or methemoglobinemia). These are described as "blue water babies". The condition appears to occur only in babies under eight weeks of age who are not breast-fed.

In my opinion one is justified in wondering whether the *immediate* and visible effect of such water on babies may not be a slow and insidious, *cumulative* effect in the case of adults. I cannot with an

easy mind think of adults drinking *for years* water that produces such serious effects on babies *after only a few days*.

The urochrome content of drinking-water must be determined

In my opinion the greatest danger of water relatively rich in nitrate does not lie in the nitrate itself. But this substance, as Hettche or Taylor recognise, is indicative of an organic pollution of the water supply and very probably of the presence of urochrome, with all the grave consequences that entails. Minimum caution requires that the estimation of urochrome in town drinking-water supplies should be made obligatory.

Urochrome in tap water could be passed on in human or in cow's milk

The question of urochrome in purified river water or in water from not very deep wells would look even more serious if Hettche's observations (155, p. 83) were confirmed. The Director of the Hamburg Institute of Hygiene is of the opinion that urochrome in drinking-water passes into milk, whether human or cow's. To my mind he offers no definite proof, but nevertheless, he is probably correct, because goitrogenic factors in a foodstuff (marrow stem kale) fed to cows pass into the milk (see p. 82). It seems logical, therefore, to suppose that a goitrogenic factor contained in water will likewise pass into the milk. This question merits the fullest attention.

From modern chemical analysis to the wisdom of the Vedas

There is, however, no cause for panic. If it should appear that some of the purifying and filtering plants in our large cities leave a certain amount of urochrome in the water, it would be easy to counteract the danger by adding a few drops of a copper salt to the water. Like so many others, this problem can be solved, but only if it is recognised and studied seriously.

One would only be applying, in a different form, the advice given three thousand years ago by that sacred book of India, the Vedas, where we read (155): "If you are not certain of the purity of your water, let it stand in a copper vase for two days before drinking it."

Relationship between goitre and cancer from the geographical and climatic point of view

Many obscure aspects of the relationship between the thyroid and cancer of other organs

THE many discussions and contradictory conclusions regarding the possible correlation between goitre and cancer (of organs other than the thyroid) were referred to above (see p. 215). The forms and causes of goitre are many, as are the forms and causes of cancer. There is a risk of comparing quite different "biological accidents", imagining that they are identical entities.

Geographical distribution of goitre and cancer in Holland

As regards the frequency of cancer, the following have already been examined:

- a geographical relationship: the iso-carcinoma map of Holland (see pp. 231-234);
- a climatic and seasonal relationship: the frequency of cancer mortality as a function of month of birth (see pp. 243, 244).

There is also a map of endemic goitre in Holland, drawn up by Hettche (155), and this is compared in Fig. 16 (facing) with the isocarcinoma map of Tromp and Diehl. One is immediately struck by the fact that on the whole, despite a few scattered irregularities, where cancer is frequent, goitre is rare.(*) The converse is also true, though sometimes less obviously.

(*) Note that in 1954 (i.e., the same year as Hettche) Spencer (354) produced a map of goitre in Holland which differs from that of the German professor. Spencer did not try to compare his map with the iso-carcinoma map, but attempted this comparison instead in Great Britain and Switzerland. He concluded that there was a geographical correlation between endemic goitre and cancer, though I myself could not distinguish it on the maps. I would rather have said the contrary was true for Switzerland.

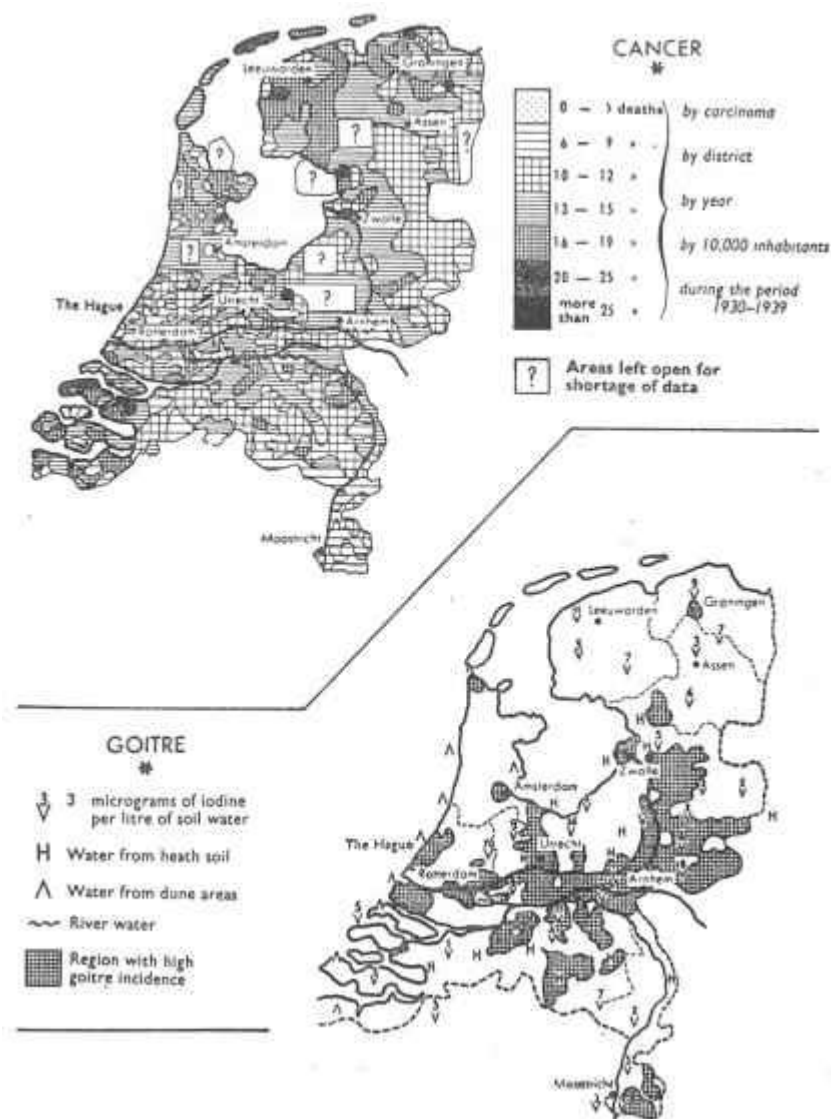


FIG. 16. Frequency of cancer and goitre in Holland as a function of the nature of the soil.

From Tromp and Diehl (373), and Hettche (155).

Cancer families and goitre families

This question of the geographical relationship of goitre and cancer is as controversial as all the other aspects of the subject.

I will restrict myself, therefore, to two personal reminiscences. I have already referred to my enquiry into goitre in two neighbouring villages in Bavaria, Aidling and Riegsee (see p. 211). The Riegsee resident who was so ready to supply me with statistical information told me, when I asked him, that he knew of several families in which cancer had been frequent but which had never suffered from goitre. He quoted one family in particular in which the father, mother and son had died of cancer, but where there had never been a case of goitre, which was exceptional in this village.

"We are obviously short of widows with £100,000"

In the Tipperary area of Ireland there is a "goitre belt", where 60 per cent of the girls were found to be suffering from simple goitre, usually of Type I (palpable, but not visible). In a maritime zone, such as Galway, on the other hand, goitre was never encountered.

While on a lecture tour of Ireland I took the opportunity of studying some of the questions connected with goitre and cancer. In this work I had the valuable support of the Irish official services, for which I should like to express my thanks.

In District X, where goitre is very widespread, my guide was the young Public Health Inspector who had been in his job for only three years, so he thought it advisable to call in the opinion of an aged doctor who had been practising in the region for thirty years, after a spell of ten years in Galway (area with no goitre). Both these men were agreed in their reply to my questions: cancer was very rare in region X. The Public Health Inspector remarked that he had only had two certificates of death from cancer in three years, a remark which brought the following confirmation from the old doctor: "I had not paid any attention, but it is a fact that in thirty years here I have not had half the number of cancer cases that I had in Galway in ten years."

And with that relentless Irish humour, in true Bernard Shaw tradition, that never misses an opportunity, he turned to the young inspector and said: "We have overlooked this rareness of cancer in our region. The fact must be made public, and then rich widows, all with their £100,000, will come and retire here, safe in the knowledge that they can end their days without being attacked by cancer. We

are obviously short of rich widows. They must no longer be reserved solely for Eastbourne."

The soil "controls" goitre and cancer

These two personal experiences are only isolated instances and cannot be considered as representing a rule. They appear, however, to confirm the phenomenon illustrated in Fig. 16 (p. 257). Caution is necessary here, but it can be said that, in regions with a *certain type* of endemic goitre, cancer (*) appears to be relatively more rare.

There is no disputing that endemic goitre is closely correlated with the soil, and so it must again be assumed that the soil "controls" the frequency of cancer.

Month of birth and frequency of goitre

As mentioned above (p. 243), the astonishing fact has emerged that cancer mortality may also be a function of the month of birth. A curve of goitre among army recruits as a function of their month of birth is available for the Munich region (Bavaria). When these two curves are compared (Fig. 17), the similarity existing between

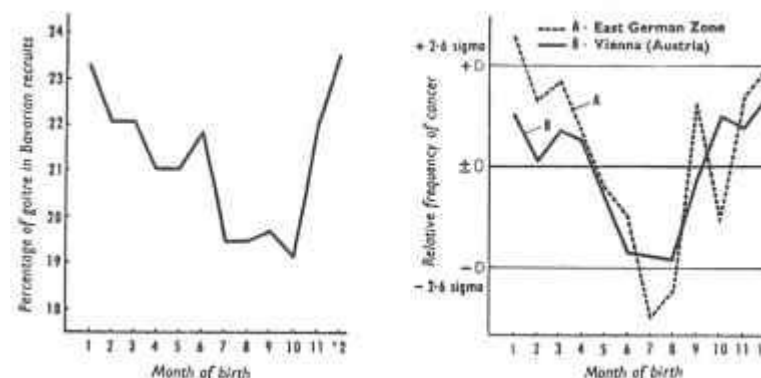


FIG. 17. Frequency of cancer and goitre as a function of month of birth.

From Dörmann (98) and Hettche (155, p. 86).

them (especially in the case of the cancer curve for Vienna) is truly amazing: minimum frequency of goitre as well as of cancer is found among persons born in July-August, maximum frequency among those born in December-January.

(*) This refers, of course, to cancer of other organs than the thyroid.

Parallelism and contrast between goitre and cancer

No general statement can be based on these two single comparisons of the positive or negative correlation between goitre and cancer. It can be said, however, that the following two-fold problem (summarised very briefly) arises:

1. A *soil* factor that favours endemic goitre is unfavourable to cancer; or conversely, a soil factor that promotes the development of endemic cancer restrains the development of goitre.
2. A factor, *seasonal* in character, favours, during the life of the foetus or suckling of the infant, *both* endemic goitre *and* cancer.

In other words:

in the case of the soil, the correlation is *negative*;
in the case of the climate, the correlation is *positive*.

It must again be stressed that these conclusions are valid only in the particular circumstances under which these observations were made.

Protection against cancer begins in the soil

Everything said in these last few chapters confirms the influence of the soil and the water emerging from it on the frequency of cancer: which, of course, does not signify that the soil is the *only* factor that controls cancer frequency. But what must be said, and said again, is that "protection" against cancer begins in the soil and depends therefore on the way in which the latter is treated and cultivated.

If the soil is overlooked in studies concerned with "*protection*" against cancer, no progress can possibly be made. This is a fact so fundamental that, before reaching the final conclusions of this work, reference will be made to a very recent American study which tried to discover why a group of human beings had been "protected" against cancer but could not arrive at any conclusion; it had forgotten the soil.

CHAPTER 65

When cancer is studied and the soil forgotten

The soil is a subject much neglected in Medical Faculties

THE attention of doctors is not greatly attracted to soil questions. It might even be said that at the present time all over the world medical scientists are engaged in investigations without giving thought for one moment to the fact that the food being consumed by their patients, or future patients, is produced by a powerful machine, widely distributed throughout the world and known as: the soil. Even if this question of the soil is less neglected in veterinary studies, it still does not receive all the consideration that it should.

Navajo Indians are rarely attacked by cancer

A typical and very interesting example may serve to illustrate the extent to which the soil is neglected by modern medical science.

There is a tribe of Indians in the United States, the Navajos, who live in a reserve straddling the States of Arizona, Utah, Colorado and New Mexico. This area, some 15 million acres in extent, supports a population of 80,000 Indians, among whom, as the doctors in the hospitals in the "Navajo Reservation" observed, cancer is extremely rare (208 cases out of 60,000 patients examined).

Vast resources harnessed to study the nutrition of the Navajos

It was rightly thought that their feeding was what "protected" these Indians against cancer, and so it was decided to investigate this aspect thoroughly. Dozens of scientists—doctors, biochemists, dietitians, etc.—from the Vanderbilt University (Tennessee), the Departments of Health of Arizona and Maryland, etc., were grouped together for this purpose.

Nothing special found in the diet

The results of the enquiry were published in 1956 in a large volume (82), the outcome of a noteworthy investigation carried out with great care.

The conclusion reached was that the diet of the Navajos was hardly any different from that of other sections of the population and that it must be assumed that it was a different racial characteristic that conferred a special resistance to cancer upon these Indians. It was stated:

"in view of the well-recognised differences between racial groups in rate of incidence of cancer and other disease, it may logically be hypothesised that a genetic influence is a more likely explanation than a dietary one."

The question of the soil producing the Indians' food was completely overlooked

This conclusion may be correct, but it would be easier to accept if all the elements involved in the diet had really been examined. Not the least attention was paid to the nature of the soil in the Reserve producing most of the food for these Indians, and in all this long report there is not the slightest reference to the nature of the soil or the methods used by the Navajos for its cultivation. Among the many branches of science represented by the team of investigators, I found no mention of agronomists or soil scientists.

The Navajos burn trees and add the ashes to their flour

The Navajos, however, seemed to have some idea that they were formed from the "dust" of their soil and that it was as well to add some of this on occasion to their maize flour. What they do is to burn cedar branches and mix the resulting ash with maize flour. Thus they are adding "mineral supplements" from their soil to the flour. As it is also stated (82, p. 9) that they supplement their home-produced commodity with flour bought in from other regions, it is possible that instinct has made them aware of the advantage of adding this "dust" from their *own* soil to foodstuffs that comes from *outside* and lack it.

The water drunk by the Navajos was not taken into consideration

Another point which struck me about this enquiry was the question of the water. The American investigators did note (82,

p. 20) that the almost exclusive drink consumed by this tribe was spring water. But no details at all are given about the composition of this water, particularly its mineral equilibrium. All that can be said here is that it did not cause goitre, because goitre is practically unknown among the Navajos (82, p. 51).

The assumption must also be made that even the drinking-water for the animals was extremely pure, because the report states (82, p. 27) that shepherds rarely carry water with them and drink at the watering-places used by their sheep.

Be that as it may, the role that water might possibly play in the resistance of the Navajos to cancer was not considered, although the reader's attention has already been drawn to the enormous importance of the mineral equilibrium of water in resistance to cancer (see pp. 245-250).

Dietetics will progress only when the soil providing foodstuffs is taken into account

This very recent study carried out by the most eminent American specialists using the most modern scientific methods has been described in detail because it is difficult to find an example more characteristic of the point stressed at the beginning of this chapter:

"Medical scientists are engaged in investigation without giving thought for one moment to the fact that food is produced by a powerful machine, widely distributed throughout the world and known as: the soil."

It is time, as I made clear at the very beginning of this book, that the entrance to every Faculty of Medicine in the world bears above its gates the inscription:

"Remember that you are only dust."

Foodstuffs are studied without considering the machine that manufactured them: which is tantamount to looking for the causes of a defect in a casting and not taking into account the blast-furnace or the raw material used in it.

Dietitians can prescribe all the diets they like. The results will be unpredictable until such time as the soils that produced the constituents of the diets are taken into account. Dietetics will progress and "*protective*" medicine will be effective only when it is remembered that the soil makes both the food and the man (see pp. 23, 24).

CHAPTER 66

*From grass to the "protective" medicine
of tomorrow***The "dusts" of the soil control the metabolism of the cells**

GRASS made it possible to obtain a "biochemical photograph" of the soil, showing clearly that the mineral elements of the soil control cell metabolism in the *animal* and consequently also the latter's vigour and health. On pursuing this study further it was found that the "dusts" of the soil likewise control the proper functioning of the cells in *Man*. Thanks to grass, therefore, the great importance of the health of *soil* for the health of *Man* has been revealed.

**Diseases are created chiefly by destroying the harmony reigning
among the elements of the soil**

What must never be forgotten is that diseases are created chiefly by destruction of the harmony existing between the soil elements. The great tragedy of modern techniques is the complete disruption of this harmony by new cultural methods. Karl Jaspers, my Professor of Philosophy at Heidelberg University when I studied there, often spoke, and with good reason, of "*Die Dämonie der Technik*" (the demoniacal character of the technical). This "*Dämonie*" brings its ravages to bear above all on the soil, the very basis of human life, and it will be the task of all agronomists, veterinarians and medical scientists of tomorrow to apply their skill to re-establishing the harmony in the soil that the "*Dämonie der Technik*" has destroyed.

"Biological suicide" by the masses in the cities

The importance of this harmony among the soil elements grows day by day as the agronomic methods being practised threaten to throw out of gear the mechanisms of the human cell.

Increasing human population and the enormous pressure being exerted by organised masses of city-dwellers on powerless agri-

cultural communities are gradually reducing the agricultural population, which is forced constantly to increase its output, producing more food, more cheaply, without any thought for its biological values. This result can be achieved only by the use of ever-greater quantities of mineral chemical fertilisers. It is impossible to go back (386, 387), and it would be undesirable, as has been shown above by the many examples of the beneficial effect that fertiliser dressings can exert on the plant and on the animal. The fertiliser, however, must be applied *judiciously*—which it is not at present. Today, indeed, three times as much of *all* the elements in the soil is being removed, but generally only *four*, or at the most seven, of these elements are being replaced.

The serious consequences of applying large quantities of nitrogenous fertilisers to a pasture over a period of fifteen years were referred to above (pp. 35-38).

The voice of the great Alexis Carrel

This seems a suitable point to draw attention to what was written by a great French scientist more than twenty years ago. In his book *L'Homme, cet Inconnu (Man, the Unknown)*, Alexis Carrel, a Nobel Prize-winner, writes (61, p. 136):

"Chemical fertilisers, by increasing the abundance of the crops without replacing all the exhausted elements of the soil, have indirectly contributed to change the nutritive value of cereals."

It can be said in more general terms that these changes affect cereals as well as grass, carrots and peaches.

The great task of "protective" medicine is to discover such changes in order to remedy them: for example, by the more judicious use of mineral fertilisers, and particularly by widening their scope so as to prevent impoverishment of the soil upsetting the metabolism of the human cells.

Only thus will the increasingly rapid development of the "diseases of civilisation", namely, cancer, nervous diseases, thrombosis, etc., be halted. Only thus will the *premature ageing* of the cells of certain organs be arrested.

**Protection against cancer is much more important and effective
than cancer therapy**

This appeal by the French scientist, who has now passed from the scene, is supported by a statement made by Professor Bauer, surgeon

at the University of Heidelberg, (*) and one of the greatest cancer specialists in Germany. In 1949 he published a large work entitled *Das Krebsproblem (The Cancer Problem)* (30), which today is still one of the most complete encyclopaedias on the subject. On p. 654 of this book he writes:

"The role of nutrition in protection against cancer (*Krebsverhütung*) has recently been confirmed by new observations (see pp. 183 and 186). We are justified in concluding that *nutrition, whatever its nature, can favour cancer or on the other hand protect against it.*"

Four years later at the Cancer Congress in Freiburg-im-Breisgau, Bauer emphatically stressed these same conclusions (31, pp. 254-255).

"Methods of protection must henceforth occupy first place in the struggle against cancer, a place well in advance of therapeutic methods."

The last hope of a great surgeon

It is not without a trace of sadness, and a very impressive sadness, that the great cancer specialist confides his conclusion to his audience (31, p. 255):

"For twenty-five years I have devoted every day of my life to the struggle against cancer. Today I am forced to admit that, whatever the difficulties in the way of its realisation, I place my last hope in *protective* measures against cancer (*Ich setze die letzte Hoffnung auf Massnahmen der Krebsverhütung*)."

These words were spoken in 1953 by an eminent surgeon, by one practising a science which alone perhaps has allowed perceptible progress to be made in the therapeutics of cancer.

Struggle with the causes instead of merely curing the consequences

Bauer's conclusion is exactly that of this book: the primary aim must be to *protect*, that is, to grapple with the causes, rather than to concentrate on curing the disease, which, after all, is only the consequence. Attention must be concentrated particularly on the principal factor in this protection: nutrition and the *soil* that creates the food.

(*) See p. 185 for another quotation from Bauer.

Philosophy of grass and of life

This is the scientific philosophy that I have evolved for myself through watching my cows at grass. Grass reveals with dazzling clarity a truth which must never be forgotten:

The soil must be kept in good health if the animal is to remain in good health. The same is true of Man. *Soil science is the foundation of protective medicine*, the medicine of tomorrow.

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ABBREVIATIONS OF REFERENCES

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 B. = Bulletin. R. = Review or Revue.
 C. R. = Comptes-rendus. Z. = Zeitschrift.

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