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TEXT-BOOK
OF
PHYSIOLOGICAL AND PATHOLOGICAL
CHEMISTRY

BUNGE

FIFTH EDITION

BARTLEY'S

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A Text-book for Medical and Pharmaceutical Students. By E. H. BARTLEY, M.D., Professor of Chemistry and Toxicology at the Long Island College Hospital; Dean and Professor of Chemistry, Brooklyn College of Pharmacy; President of the American Society of Public Analysis; Chief Chemist, Board of Health of Brooklyn, N. Y. Revised and Improved. With Illustrations, Glossary, and Complete Index. 12mo.

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PUBLISHERS

TEXT-BOOK
OF
PHYSIOLOGICAL AND PATHOLOGICAL
CHEMISTRY

BY

G. BUNGE

PROFESSOR OF PHYSIOLOGICAL CHEMISTRY AT BÂLE

SECOND ENGLISH EDITION

TRANSLATED FROM THE FOURTH GERMAN EDITION
BY
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AND EDITED BY
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PROFESSOR OF PHYSIOLOGY IN UNIVERSITY COLLEGE, LONDON

PHILADELPHIA
P. BLAKISTON'S SON & CO.
1012 WALNUT STREET
1902

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EDITOR'S PREFACE

Professor Bunge's Lectures on Physiological Chemistry have had a great influence on physiological thought both here and abroad. Representing as they do the ideas which have produced throughout many years discoveries of fundamental importance in the school of Schmiedeberg, they have served to spread the method of thought of that school and to render more effective the work of men in other laboratories. Among these researches, I might especially mention those of Schmiedeberg alone or in conjunction with his pupils on the mechanism of oxidation in the body, on the occurrence of synthetic processes in the body (*e. g.*, the synthesis of hippuric acid in the kidney, worked out by Bunge and Schmiedeberg), Schröder's work on the formation of urea, Minkowski and Naunyn on uric acid, Minkowski on the production of diabetes by extirpation of the pancreas, besides researches into the chemistry of nucleins, of chondrin, the mucins (Leathes), and many other subjects of bio-chemical interest.

These Lectures have also the merit of being written by a man who was philosopher, mathematician and chemist before he was a physiologist, and who, being thus in a position to grasp the general bearings of his subject, has succeeded in making the dry bones of physiological chemistry interesting even to the beginner.

It was with great pleasure that I undertook to edit a new translation by my wife of the latest German Edition, as I consider it eminently desirable that these suggestive Lectures should be available for those students and medical men who are not familiar with German.

I would here especially endorse the author's recommendation to students to go back whenever possible to the original

ASP May 19/20

papers, copious references to which form a prominent feature of these Lectures. A careful study of a few of the classic researches in their original form will do more to acquaint a man with the spirit of physiology than the most arduous perusal of text-books. It is essential to the healthy development of the thinking powers that they should have some work to do, and not be nourished solely on a diet of already digested material.

Although the conclusions drawn by the author are occasionally not those which would commend themselves to the majority of physiologists, I have thought it better to indicate in a footnote the existence of other opinions rather than interfere in any way with the vitalistic mode of thought which gives these Lectures much of their interest and individuality. Such additions are distinguished by square brackets.

ERNEST H. STARLING.

LONDON, *March*, 1902.

PREFACE TO THE FIRST EDITION

It has not been my intention to enlarge the present volume beyond the scope of a text-book; all disconnected facts and mere descriptive matter have therefore been omitted. In original research, every fact, however isolated it may at first seem, may prove of inestimable value as a starting-point for fresh ideas and inquiries. For this reason, an exhaustive account of all facts is both valuable and necessary in a hand-book. But a text-book should merely seek to initiate and interest the student, and to acquaint him with the principal achievements of investigation in biological sequence. A mass of statements and details would weary and disgust the beginner, and might deter him from pursuing the subject altogether. But if interest once be awakened by a suggestive though inadequate treatment of the subject, the deficiencies may readily be supplied by recourse to the hand-books, or, better still, by a careful perusal of the original works.

Descriptions of analytic methods have also for the most part been avoided, as they would have interrupted the main narrative, and as we already possess numerous standard works on chemical analysis in physiology and pathology, such as those by Hoppe-Seyler, Leube and Salkowski, Neubauer and Vogel. With the aid of such teachers as these, analysis should be learnt and practised in the laboratory.

On the other hand, I have endeavored to introduce everything that is at present ripe for a connected account. Especial care has been bestowed on the references. The original memoirs quoted have been so chosen that, with them as a basis, the reader who is desirous of pursuing the study of physiological chemistry will readily be able to find his way through its remaining literature, and will also have his attention drawn to those works which were beyond the scope of my subject.

If my lectures succeed in inducing the study of the original sources, my aim will have been attained. Of what use would it be to the medical student to learn up an exhaustive treatise on physiology? In a few years he would be no wiser than before. In science, it is imperative that all academic teaching should be so directed as to render the student capable of following its progress. For this, a thorough knowledge of the exact sciences, physics and chemistry, is requisite; he will then be in a position to read physiological works, which he should be led to weigh and discuss critically. No one will ever regret time and trouble spent in this way. Later in life, he will find that he can always increase his knowledge, and that all medical work will be the easier for it. An intimate acquaintance with the exact natural sciences would shorten and simplify medical study.

The object I have kept in view throughout these lectures has been to enable the beginner to refer at once to the most valuable passages in the original works, whenever his interest has been excited in any question of physiological chemistry.

G. BUNGE.

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LECTURE I

INTRODUCTION—VITALISM AND MECHANISM

By way of introduction, I may be allowed to lay before my readers the views I hold on the aims and prospects of modern physiological research. We read in numberless physiological papers, and in the introduction to almost every text-book of physiology, that the object of physiological inquiry is to explain the phenomena of life by physical and chemical, and therefore ultimately by mechanical laws. A physiologist of the present day would be regarded as lacking both in intelligence and industry, were he to take refuge, as at one time the 'vitalists' did, in the assumption of a special 'vital force' as a means of explaining biological problems. I can only accept this view in a modified form, and with the understanding that no explanation is offered by a mere term. I regard 'vital force' as a convenient resting-place where, to quote Kant, "reason can repose on the pillow of obscure qualities."

But I cannot assent to the doctrine which some opponents of vitalism maintain, and which would have us believe that in living beings there are no other factors at work than simply the forces and matter of inorganic nature. We certainly cannot recognize more than these forces, owing to the limitation of our powers, since in the observation of both organic and inorganic nature we always make use of the same organs of sense, which react only to certain forms of motion. A form of motion transmitted to the brain by the fibers of the optic nerves arouses in us the consciousness of light and color; the consciousness of sound is due to another form of motion transmitted by the auditory nerve; all our sensations of taste and smell, of temperature and touch, are due to forms of motion. At least this is what physics teaches us; these appear to be at present the most fruitful hypotheses. It would indeed be a lack of intelligence to expect, with the same senses, to make discoveries in living nature of a different order to those revealed to us in inorganic nature.

But for the study of organic nature we possess one additional sense, our 'internal sense': the power of studying and observing the conditions and processes of our own consciousness. To hold that this also is a variety of motion is, in my opinion, an untenable doctrine. The simple fact that many conditions of consciousness have no relation to space is opposed to such a view. Only what consciousness has acquired by certain senses, sight, touch, muscular sense,[1] is related to space. All other sensations, emotions, passions, and an unlimited number of ideas have no relation to space, but only to time. We cannot here, then, speak of a mechanism. It might be suggested that this is only an apparent difference—that in reality these also have spatial qualities. But such an opinion cannot be sustained. We suppose that objects which we perceive with our senses have spatial qualities simply on the ground that, so far as we can observe them by means of our senses, touch and sight, they seem to possess them. But for the whole world of our internal sense, we have not even this apparent reason, so that we cannot admit that there is any ground for such a supposition.

Therefore the deepest insight we can gain into the most essential part of our nature shows us something quite different, shows us things which are without spatial qualities, and processes which can have nothing to do with mechanism.

The opponents of vitalism, those who support the mechanical explanation of life, usually seek to justify their views by saying that the further physiology advances, the more does it become possible to explain, on physical and chemical grounds, phenomena which have hitherto been regarded as associated with a special vital force; that it is only a question of time; that it will finally be shown that the whole process of life is only a more complicated form of motion regulated solely by the laws which govern inorganic nature.

But to me the history of physiology teaches the exact opposite. I think the more thoroughly and conscientiously we endeavor to study biological problems, the more are we convinced that even those processes which we have already regarded as explicable by chemical and physical laws, are in reality infinitely more complex, and at present defy any attempt at a mechanical explanation.

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[1] The ideas of space, which are connected with the sensations of sight and touch, are possibly only brought about by the complex muscular apparatus, which plays a part in all the functions of the organs of sight and touch. This is also true of the so-called 'common sensations.' The ideas of space may be due to the sensory fibers of the muscular nerves only. This view was first upheld by Steinbach ("Beiträge zur Physiologie der Sinne," Nürnberg, 1811), and contested by Joh. Müller ("Zur vergleichenden Physiologie des Gesichtssinnes," p. 52: Leipzig, 1826), but, in my opinion, on unsatisfactory grounds. Joh. Müller was a supporter of Kant's doctrine of space, which likewise appears to me untenable.

Thus we have been satisfied to account for the absorption of food from the alimentary canal by the laws of diffusion and osmosis. But we now know that, as regards osmosis, the wall of the intestine does not behave like a dead membrane. We know that the intestinal wall is covered with epithelium, and that every epithelial cell is in itself an organism, a living being with the most complex functions; we know that it takes up food by the active contraction of its protoplasm in the same way as observed in independent naked animal cells, such as amebæ and rhizopods. Observations on the intestinal epithelium of cold-blooded animals have made it obvious that the cells grasp the particles of fat contained in the food by means of protoplasmic processes which they send out; that they incorporate the fat-globules with the protoplasm of the cell, which finally passes them on to the commencement of the lacteals.[1] As long as this active intervention of cells was unknown, it was impossible to understand the remarkable fact that, although the minute drops of fat were able to pass through the intestinal wall, yet finely divided pigments, intentionally introduced into the intestine, remained quite unabsorbed. At the present time we know that all unicellular organisms possess the power of selecting their food, of taking up the useful and rejecting the useless substances. In this connection, I may relate an interesting observation made by Cienkowski[2] on an ameba, called the Vampyrella.

The *Vampyrella Spirogyræ* is a minute red-tinged cell devoid of any special limiting membrane, and apparently quite structureless. Cienkowski could find no nucleus in the cell, and the small granules observed in the protoplasm were probably only residues of nutrient matter. This minute mass of protoplasm will take but one form of food, a particular variety of algæ, the Spirogyra. It can be observed to send out pseudopodia and to creep along the Confervæ until it meets with a Spirogyra; then it affixes itself to the cellulose coat enclosing one of the cells of the latter, dissolves the coat at the point of contact, sucks in the contents of the cell, and travels to the next to repeat the process. Cienkowski never saw the Vampyrella attack any other class of algæ, or even

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[1] R. Wiedersheim, has given an account of the older literature, together with his own investigations on this subject in the "Festschrift der 56. Versammlung deutscher Naturforscher und Aerzte, gewidmet von der naturforschenden Gesellschaft zu Freiburg i. B." Freiburg und Tübingen: 1883; and G. H. Theodor Eimer, *Biolog. Centralbl.*, vol. iv. p. 580: 1884; and Heidenhain, Pflüger's *Arch.*, vol. xliii., Suppl.: 1888.

[2] L. Cienkowski, "Beiträge zur Kenntniss der Monaden," *Arch. f. mikrosk. Anatomie*, vol. i. p. 203: 1865.

take up any other substance; Vaucheriæ, Œdogoniæ, purposely placed before it, were always rejected.

Another monad, the *Colpodella pugnax*, was observed by Cienkowski to feed exclusively on Chlamydomonas: "it punctures, as it were, the latter, absorbs the escaping chlorophyl, and departs." "The behavior of these monads," says Cienkowski, "in their search after food and in their method of absorbing it, is so remarkable, that one can hardly avoid the conclusion that the acts are those of conscious beings."

If this power of selecting food is possessed by the structureless mass of protoplasm, why should it not also be a function of the epithelium of our intestine? Just as the Vampyrella picks out the Spirogyra from amongst all other algæ, so do the epithelial cells of our intestines select the fat-drops and reject the pigment-granules. We know that the epithelium of the intestine prevents the absorption of a whole series of poisons, in spite of the fact that the latter are easily soluble in the gastric and intestinal juices. Indeed, we know that these poisons when injected into the blood, are excreted by the intestine.

It was likewise once thought that the activity of glands and the processes of secretion were in the main explicable by osmosis. But we now know that here too the epithelial cells play an active part. Here again we find the same mysterious power of selection, of picking out certain constituents of the blood, of altering them by processes of synthesis and decomposition, of sending some into the ducts of the glands, and others back into the lymph and blood. The epithelial cells of the mammary gland collect all the inorganic salts from the blood—which has a totally different constitution—in the exact proportion required by the infant, that its growth and development may assimilate it to its parents. These phenomena cannot at present be explained by the laws of diffusion and osmosis.

All the cells of our tissues possess the same wonderful powers as the epithelial cells of the alimentary canal and of glands. Consider the mode of development of our organism: all tissue elements are produced from a single ovum, and in proportion as the cells increase by segmentation, they become differentiated on the principle of the division of labor; every cell acquires the faculty of rejecting some substances, of attracting others and storing them up, thereby attaining the composition necessary for the due fulfilment of the functions it has to perform. But it is hopeless to offer a chemical explanation of this process.

Just as little has it been possible, in other branches of physiology besides that of nutrition, to refer any single vital process to the laws of chemistry and physics.

We have sought to explain the functions of nerve and muscle by the laws of electricity, and must now admit that electrical processes have been demonstrated with certainty to occur in the living organism only in a few fishes; or even if we grant that electrical currents have been decisively proved to exist in muscles and nerves, we are bound to confess that the explanation of the functions of nerve and muscle is but slightly advanced thereby.

It may be suggested that the physiology of the special senses offers a field for precise physical explanations. It is true that the eye is a physical apparatus, an optical apparatus, a camera obscura. The image on the retina is formed by the same unchanging laws of refraction as the image on the sensitive plate of a photographer. But it is not a vital process. The eye is absolutely passive in the matter. The image on the retina is formed in an eye separated from the body and dead. The development of the eye is a vital process. How is this complex optical apparatus formed? Why do the cells arrange themselves so as to produce this wonderful structure? This is the great problem towards the solution of which nothing has yet been done. The succession of events in development may indeed be observed and described, but of the wherefore, the causal connection, we know absolutely nothing. The process of accommodation is a vital process. Here again we have to deal with the old unsolved question of muscle and nerve. The same is true of the other organs of sense. We can explain physically nothing but those processes in which the organ is quite passively set in vibration by external impulses.

The same is true of all other branches of physiology. We have endeavored to explain the phenomena of the circulation of the blood on a physical basis. The blood is certainly subject to the laws of hydrostatics and hydrodynamics, but it is perfectly passive as regards circulation. No one has hitherto been able to explain the active functions of the heart and muscular wall by a reference to physical laws. An attempt has been made to explain the gaseous interchange which occurs in the lungs, by the laws of aërodynamics, of absorption and diffusion, and it is possible that the attempt may be successful. Here again, however, we are not dealing with a vital phenomenon. The respiratory bellows being set into motion, the gases move in and out according to the unchangeable laws of dynamics, but we have to inquire how the respiratory bellows are formed and maintained, and how they are able to carry out their movements. Throughout the whole process the gases play only a passive part.

I maintain that all the processes of our organism capable of explanation on mechanical principles are as little to be regarded as vital phenomena as the rustling of leaves on a tree, or as the movement of the pollen when blown from stamen to pistil. Here we have a form of motion essential to the phenomenon of life, and yet no one would consider it a vital act, simply because the pollen is quite passive under it. It does not in the least alter the main point at issue, whether the source of motion is formed by the kinetic energy of the wind, or by the sunlight which induces the wind, or by the latent chemical energy into which the sunlight has been converted.

The mystery of life lies hidden—in activity.[1] But the conception of activity has come to us, not as the result of sensory perceptions, but from the study of our own internal consciousness. We transfer to the objects of our sensory perception, to the organs, to the tissue-elements and to every minute cell, something which we have acquired from our own consciousness. This is the first attempt towards a psychological explanation of all vital phenomena.

If, as it thus appears, it is impossible to explain vital phenomena by the help of physics and chemistry alone, we must inquire what the other auxiliaries to the science of physiology—the morphological sciences, anatomy and histology—can do for us.

I hold that there is at present but little likelihood of attaining our aim by their means. For when we have, with the aid of scalpel and microscope, carried our anatomical analysis to its utmost limit, to the simple cell, we still have the great problem to face. The most simple cell—a formless, structureless, minute mass of protoplasm—exhibits all the essential processes of life, as nutrition, growth, reproduction, movement, reaction to stimulation ; it even displays functions which act at least as a substitute for the psychical powers of higher organisms. You will remember that it is so in the case of the Vampyrella, and I should like to call your attention to the still more remarkable observations which Engelmann has made on the Arcellæ.[2]

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[1] Activity and life are perhaps two words for the same idea, or rather two words to which no definite idea is attached. And yet these vague terms are all that we have at our command. Here we approach the most difficult problems, which have foiled all attempts at solution.

[2] Th. W. Engelmann, "Beiträge zur Physiologie des Protoplasmas," Pflüger's *Arch.*, vol. ii. p. 307 : 1869. Compare also vol. xxv. p. 288, Note I. 1881; vol. xxvi. p. 544, 1881; vol. xxx. pp. 96, 97, 1883; and Max Verworn, Pflüger's *Arch.*, vol. liii. p. 140, 1893.

The Arcellæ are also unicellular organisms, but they are more complex than the Vampyrella, because they have a nucleus and a shell. This shell has a convex-concave form. In the middle of the concave side of the shell is an opening from which the pseudopodia project, appearing as clear protuberances at the edge of the shell. If a drop of water containing Arcellæ be placed under the microscope, it often occurs that one of them falls on its back as it were, *i. e.*, with the convex side downwards on the slide, so that the pseudopodia which appear at the edge of the shell cannot reach any support. It is then observed that, near the edge on one side, minute bubbles of gas make their appearance in the protoplasm; this side consequently becomes lighter and floats up, so that the animal now rests upon the opposite sharp edge. It is now able, by means of its pseudopodia, to grasp the slide and thus completely to turn over, so that all the pseudopodia are downwards. The gas-bubbles now disappear, and the animal crawls away. If a little water containing Arcellæ be dropped on the under side of a cover-glass, and the latter be placed in a small gas-chamber, it is observed that the animalcules at first sink to the bottom of the drops. If they find nothing to lay hold of, large bubbles of gas are developed in the protoplasm, and as they are thus rendered specifically lighter than the water, they rise in the drops. If they reach the surface of the glass in such a position that they cannot attach themselves to it by their pseudopodia, the gas-bubbles are diminished on one side or increased on the other (sometimes simultaneously on both), until a tilting takes place and the edge of the shell comes in contact with the glass, and they are thus enabled to turn over. When once this is accomplished, the bubbles again disappear, and the animal can now crawl freely about the glass. If the Arcellæ are carefully detached by means of a needle, they at first fall to the bottom, and then go through the same proceedings anew. Whatever attempt may be made to put them into an inconvenient position, they are always able, by the development of gas-bubbles of appropriate size and at the proper spot, to right themselves, so that they acquire a position favorable to locomotion; and the attainment of this object is always followed by the disappearance of the bubbles. "It cannot be denied," says Engelmann, "that these facts point to psychical processes in the protoplasm."

Whether this view of Engelmann's is justified or not, I do not venture to decide. I will even unreservedly admit that these remarkable phenomena may find a mechanical explanation. I have brought these facts to your notice merely in order to show you what complex manifestations of life we meet with, in cases where microscopical investigation has already reached its limit, and how little it has at present been possible to explain any single vital process on purely mechanical grounds. For the cells of which our body is composed exhibit processes which are at least as complicated as those of the simple organisms. Every one of the innumerable microscopic cells of which our body is made up is a microcosm, a world in itself.

It is a well-known fact that through one single spermatozoön, through this minute cell, five hundred millions of which would hardly occupy one cubic millimeter, all the physical and intellectual peculiarities may be transmitted from father to son, or, even skipping the son, may again, by the agency of one single minute cell, reappear in the grandson. If this is really a mechanical process, how wonderful must be the molecular structure, how complicated the interchange of forces, how intricate the forms of motion, in this small cell which shall direct all subsequent forms of motion, and the mode of development for generations! And how shall this minute structure transmit mental qualities? Here we are utterly abandoned by physics, chemistry, and anatomy.

Many centuries may pass over the human race, many a thinker's brow be furrowed, and many a giant worker be worn out, ere even the first step be taken towards the solution of this problem. And yet it is quite conceivable that a sudden flash of light may illumine the darkness. You would misunderstand me, were you to take my exposition as a confession that I imagine that science has impassable boundaries. Science will continue to ask and to answer even bolder questions. Nothing can stop its victorious career, not even the limitations of our intellect. This too is capable of being made more perfect. There is no rational ground for thinking that the continuous progression, development, and ennoblement of type which has been going on for centuries on this planet, should come to an end with us. There was a time when the only living creatures were the infusoria floating in the primeval sea, and the time may come when a race may dominate the globe as superior to ourselves in intellectual faculties as we are to the infusoria.

We must therefore unreservedly admit that the stupendous difficulties which at present beset physiological investigations may finally be overcome. But for the moment it is not apparent how any further progress of importance can be made with the help of chemistry, physics, and anatomy only. The smallest cell exhibits all the mysteries of life, and our present methods of its investigation have reached their limit.

But we may improve our methods, we may acquire microscopes of still higher power than those we now possess. The cell which at present appears to be without structure, may show a nucleus when treated with some new stain. And the nucleus itself displays a structure so complex that it will soon require the entire attention of numerous observers for its adequate investigation and description. But unfortunately a complex structure is no explanation; it only offers a new problem as to its mode of origin. And moreover how little does our knowledge of this structure help us to understand even the simple processes observable in the Vampyrell and the Arcella!

For all this, physiological inquiry must commence with the study of the most complicated organism, that of man. Apart from the requirements of practical medicine, this is justified by the following reason, which leads us back to the starting-point of our remarks: that in researches upon the human organism we are not limited to our physical senses, but also possess the advantage afforded by the 'internal sense,' or self-observation. In fact we may in this way approach the problems of physiology from two sides, just as in mining or tunnelling the workmen excavate from two directions, until those on one side hear through the intervening stone the strokes of the hammers of those on the other.

To the clear recognition of the value of this method, which enables us to attack the problem from two sides, is due Johannes Müller's great discovery of the law of the "specific energy of the senses," which is without doubt the greatest achievement both of physiology and psychology, and the exact basis of all idealistic philosophy.[1] I mean the simple law, that the same stimulus, the same external phenomenon, acting on different organs of sense, always produces different sensations; and that different stimuli acting on the same organ of sense always produce the same sensation. The phenomena of the outer world therefore have nothing in common with the sensation and ideas they call forth in us, and the states and processes of our own consciousness are alone immediately subject to our observation and recognition.

This simple truth is the greatest and deepest ever thought

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[1] In the disputation for his doctorate, Joh. Müller maintained the thesis: "Psychologus nemo nisi Physiologus." The time will come when the converse thesis: "Physiologus nemo nisi Psychologus" will stand in no need of defence.

out by the human intellect, and leads us at once to a complete understanding of what constitutes the essence of vitalism. The essence of vitalism does not lie in being content with a term and abandoning reflection, but in adopting the only right path of obtaining knowledge which is possible, in starting from what we know, the internal world, to explain what we do not know, the external world.

The opposite and erroneous view is adopted by mechanism, which is no other than materialism; it starts from the unknown, the external world, to explain the known, the internal world.

The physiologist is continually being driven back to materialism by the fact that in psychology no attempt has yet been made to attain an exactness to which the studies of physics and chemistry have accustomed us. It cannot be denied that, although nothing is so immediately under observation as the conditions and processes of our own consciousness, it is precisely on this subject that our knowledge is most vague and uncertain. There are numerous reasons for this. The object is more complicated, the qualities are much more numerous, than in the outer world; moreover, the states and processes in our consciousness are ever undergoing rapid variations; and, finally, we possess at present no means of quantitatively estimating the objects of our internal sense.

So long as psychology remains in this condition, we cannot arrive at satisfactory explanations of vital processes. In most branches of physiology, there is nothing to be done but to proceed along the same mechanical lines. This method is undoubtedly valuable; we must endeavor to advance as far as possible by the sole help of chemistry and physics. What these sciences fail to achieve will stand out more prominently, and thus the mechanical theories of the present will assuredly carry us eventually to the vitalism of the future.

The views put forward here have been attacked from various quarters, *e. g.*, by R. Heidenhain,[1] E. du Bois-Reymond,[2] Max Verworn,[3] A. Mosso,[4] &c.

All the objections raised by these authors can be summed up in the single sentence with which I began my discussion of the subject, viz., "It would indeed be a lack of intelligence to

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[1] Heidenhain, Pflüger's *Archiv.*, vol. xliii.; Suppl., pp. 61–64, 1888. See also my reply to the same, Pflüger's *Archiv.*, vol. xliv. p. 270, 1889.

[2] E. du Bois-Reymond, *Sitzungsb. d. k. preuss. Akad. d. Wiss. z. Berlin*, June 28, 1894.

[3] M. Verworn, "Allgemeine Physiologie," p. 50, Jena, 1895.

[4] A. Mosso, *Revue Scientifique*, 4th series, vol. v. p. 1, Jan. 4, 1896.

expect, with the same senses, to make discoveries in living nature of a different order to those revealed to us in inorganic nature" (*vide* p. 2).

These authors have left untouched the central point of the whole question, viz., the impossibility of giving a mechanistic explanation of psychical processes, and have forgotten that these processes form the *immediate* object of our experience, the most real of the real.

It is quite open to any one who objects to the term vitalism to replace it by another, such as idealism, scepticism, empiricism; but that will not alter my contention. I have only shown how the metaphysical speculations and dogmas are in direct variance with the immediate results of observation and experience, *i. e.*, empirical psychology. The hypotheses on which the mechanistic explanation of natural phenomena is based, such as the atomic theory, the wave theory of light, the mechanical theory of heat, are all of them purely metaphysical speculations, *i. e.*, attempts to gain an insight into the essential nature of things as they are, in contradistinction to that which they appear to us to be. Such hypotheses can only be arrived at by projecting certain conceptions of our inner consciousness into the outside world—conceptions such as those of space, time, quantity, number, force. So far we have not found it any advantage to project in this way other of our conceptions, although some philosophers have made such an attempt. The physicist wisely limits himself to measuring the *quantity* of objects, and does not attempt to form a judgment as to their quality.

Now however the mechanists come and, crab-like, reverse the whole process. Having begun by ascribing certain qualities, which were a pure product of their inner consciousness, to external things, they proceed to use the same conceptions to explain all vital phenomena, and imagine that by help of these threadbare and scanty conceptions they have explained the manifold activities of the inner world of consciousness.

In fact we have no grounds for assuming that our internal world, the world of consciousness, is necessarily and entirely bound up with certain parts of the brain. For we must remember that our consciousness arises by inheritance through a simple cell, from which, by repeated division, all the cells and tissues of our body are derived, including those of the brain and cerebral hemispheres, and other parts of the nervous system. Now the history of the evolution of function must run parallel with that of the evolution of structure. We cannot indeed suppose that, as we trace the animal kingdom downwards to the unicellular organisms, the conscious life of the individual ceases at that exact point where a brain is no longer present, or even where we can no longer make out a specially differentiated nervous system. May it not be possible that every cell and every atom is really a conscious being, and that all life is conscious life?

LECTURE II

THE CIRCULATION OF THE CHEMICAL ELEMENTS[1]

The object of physiological chemistry is to investigate the chemical processes of the living organism, and to consider the relation of these processes to vital phenomena. We shall confine ourselves to a consideration of these processes as they occur in man and the higher animals. It may appear erroneous to commence the study of the most complex organisms before obtaining a general knowledge of the chemical processes of the more simple; but since no physiological chemistry of the latter as yet exists, there is no choice left to us. The little that is known on this subject will be introduced, as occasion offers, when we come to discuss the metabolism of the higher animals.

Before we approach our subject, we must consider the various chemical elements and forces concerned in vital manifestations, as they present themselves in organic and inorganic nature. Nature must be considered as a whole if she is to be understood in detail; there must be a clear comprehension of the great unchanging laws which are equally applicable to living and inanimate things.

Twelve chemical elements enter into the composition of all living beings without exception: carbon, hydrogen, oxygen, nitrogen, sulphur, phosphorus, chlorin, potassium, sodium, calcium, magnesium, and iron.

Carbon occurs, on the surface of our planet, chiefly united with oxygen in the form of carbonic acid. Of this only a small part exists free in the atmosphere, or absorbed in water. The greater part is united with such bases as lime and magnesia, and forms gigantic strata of the earth's crust. Only a comparatively small amount of carbon occurs in a free state as

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[1] The beginner who desires to make himself more fully acquainted with the subject of the present chapter is particularly recommended to study Liebig's great work, "Chemistry in its Applications to Agriculture and Physiology," 1840, 8th edit., 1865. The scientific enthusiasm which our great teacher imparted during his life to all who came into contact with him still speaks from every page of this work. Those who wish to familiarize themselves with more modern achievements should read Adolf Meyer's "Text-book of Agricultural Chemistry" (Heidelberg, 1886), in which will be found a full account of the original literature on the subject.

coal, and a still smaller quantity as graphite and diamond. Coal is, as we well know, the residue of plants, and plants derive their carbon from the carbonic acid of the atmosphere. Apart then from graphite and diamond, the mode of formation of which is still unknown, it may be said that all the carbon on the earth is or has been in the form of carbonic acid, and that carbonic acid is the compound through which carbon must always pass in its innumerable metamorphoses. It is in this form that carbon appears in the cycle of life; in this form alone it is taken up by plants and converted into the numerous combinations of which they are composed. Carbon is introduced into the animal organism as vegetable food, and is excreted either as carbonic acid or in the form of compounds, such as urea, which very rapidly decompose outside the organism, and yield carbonic acid. Carbon then leaves the cycle of life in the same form in which it entered, and returns to the atmosphere to repeat the process anew.

HYDROGEN is found only in traces as a free gas. In inorganic nature it occurs almost exclusively in the form of water, but a minute quantity appears as ammonia. Hydrogen is taken up by plants in the form of water and ammonia only; it enters into the constitution of the organic compounds of the plants which serve as food for animals; it leaves the animal organism again in the form of water and ammonia, or in the shape of compounds which rapidly split up into these two bodies.

OXYGEN is the most widely distributed of all elements on the surface of the globe; it forms nearly one-fourth by weight of the atmosphere, eight-ninths of the weight of water, and about half the weight of the earth's crust, which is made up almost exclusively of oxygen-compounds. Oxygen is the only element which enters the living organism in a free state, but it does so only in part, and in the case of plants only to a very small extent. The chief bulk of the oxygen enters the organization of plants as water and as carbonic acid. By the aid of sunlight, the plants split off from these combinations a part of the oxygen, and form compounds richer in carbon and hydrogen, which as food-stuffs are taken into the animal body, where they again unite with oxygen, and are returned as carbonic acid and water to the air.

By this antagonism between the animal and vegetable kingdoms, the balance of carbonic acid and oxygen is maintained in the atmosphere: the plant yielding the oxygen which the animal requires, while the animal in its turn gives out the carbonic acid needed by the plant.

We may now ask whether this balance will always be maintained. Even should it not be disturbed by vital processes, may there not be agents at work in inorganic nature, which, by their action on the atmosphere, may increase or diminish those of its constituents necessary to existence?

As regards carbonic acid, the geologists are of opinion that there was formerly a larger amount in the atmosphere. What are the causes of this diminution? are they still at work? and have we to look forward to a continuous decrease in the bulk of this gas?

One of the causes of the diminution of carbonic acid is not far to seek, *i. e.*, the formation of coal strata from plants which in their turn have derived their carbon from the carbonic acid of the atmosphere. At the same time, the amount of carbon taken up in this way appears to be comparatively small. And even if the formation of coal is still going on under the sea, on the other hand carbonic acid is being unceasingly returned to the atmosphere from thousands of chimneys. We need scarcely fear a diminution of carbonic acid from this cause. But there is another one of far greater importance: I mean the displacement of the silicic acid from the stone of the earth's crust by the carbonic acid of the atmosphere—the union of carbonic acid with the bases previously existing as silicates. The rocks, which form the solid crust, consist principally of silicates and carbonates—of compounds of silicic and carbonic acids with lime, magnesium, oxid of iron, and alkalies. Now each acid is always trying to prevent the other from combining, and to unite itself with the basic constituents. Silicic acid and carbonic acid are "the two great powers in the construction of the earth," and are always at war with each other, with alternate victory and defeat on each side. As soon as the carbonic acid succeeds in obtaining complete mastery over the silicic acid, all organic life must cease on our planet.

The chemical affinity of carbonic acid to the basic constituents of the rocks is closer than that of the silicic acid, in the cold and in presence of water; the carbonic is the more powerful acid on the earth's surface, where it is obtaining a slow but sure victory. Every wave breaking against the cliffs, every ripple which washes the flinty bed of the river, every drop of rain which falls to the ground contains carbonic acid in solution, and slowly but surely destroys the hardest rock; the carbonic acid unites with the basic constituents, and the displaced silicic acid, combined with the residue of the bases, sinks to the bottom of the water, where as clay or sandstone it gradually forms massive strata of the earth's surface. But the carbonic acid, united with lime or magnesium, is likewise precipitated, mixed either with part of the decomposed silicates in the form of marl, or in separate strata as limestone and dolomite. Half the entire weight of the thick calcareous strata, which compose a very large part of the earth's crust, consists of carbonic acid, derived from the atmosphere, and which has apparently been withdrawn for ever from the cycle of life.

But the struggle between the two acids wears another aspect in the interior of the earth. At the higher temperature which prevails there, the silicic acid is the more powerful. In the depths of the earth it attacks the carbonates, and the carbonic acid which is driven off escapes into the atmosphere. This carbonic acid is continually issuing from all active volcanoes, and also from other cracks and fissures in various parts of the earth. The quantity which is thus returned to the atmosphere cannot be determined, but it seems probable that it is much less than what is constantly being removed in the form of chalk and carbonate of magnesia. If it is true that our planet is steadily becoming cooler and its crust thicker, the factor which aids the silicic acid, the warmth of the earth itself, must continually decrease, and thus leave nothing to dispute the rule of carbonic acid; hence organic life must terminate.

In like manner as carbonic acid, a second constituent of the atmosphere, oxygen, is constantly becoming fixed in the crust of the earth, and thus removed from the cycle of vital phenomena. The constituent of the earth's crust which binds it is the ferrous oxid resulting from the decomposition of certain silicates. This becomes oxidized to ferric oxid, which, as is well known, forms by itself considerable strata, and occurs in still larger quantities mixed with other materials, as clay, loam, sandstone, and shale. One-third of the oxygen in these huge masses of ferric oxid is derived from the atmosphere. A part of this oxygen may return to the atmosphere, for, when the oxid of iron comes into contact with decomposing organic substances, the latter abstract part of its oxygen. As a result of the oxidation of the organic substances, carbonic acid is returned to the atmosphere, where it may again be decomposed by plants, thus liberating oxygen. But this activity of plants is the only process by which oxygen is set free on the earth's surface, and it is very questionable whether it is of itself sufficient to counterbalance the consumption of oxygen in respiration, putrefaction, combustion, and oxidation of the compounds of iron and sulphur.

It thus appears that a substance of great importance in the nutrition of plants, free carbonic acid, and a substance essential to the maintenance of all organic life, free oxygen, are continually diminishing, and that the time is slowly but surely approaching when the conditions necessary for our existence will no longer prevail, and when all life will become extinct on this planet.

We will now turn our attention to the NITROGEN, the fourth and last of the elements which organic nature derives from the atmosphere directly or indirectly. Nitrogen is characterized by its small affinity for other elements. For this reason the greater part of the nitrogen is found in a free state; it forms four-fifths of the atmosphere. Only a minute portion is found in inorganic nature in the form of compounds: this is the nitrogen of ammonia, and of its products of oxidation, nitrous and nitric acids. Nitrogen enters organic nature in the form of these compounds only. The great bulk of free nitrogen has no part in vital processes, for the plant cannot assimilate it. So far the assimilation of atmospheric nitrogen has been proved to occur only in certain bacteria.

Now, since the quantity of fixed nitrogen existing in nature is very small, and since plants cannot utilize the other constituents of their food unless an appropriate quantity of fixed nitrogen be taken up at the same time, it is obvious that the total number of organic beings which can simultaneously exist on the earth must depend in the first instance on the amount of fixed nitrogen available. It is therefore a question of the greatest interest to know by what means the amount of fixed nitrogen is increased or diminished.

The process of life itself does not alter the sum total of fixed nitrogen. Nitrogen is taken up by the plants as ammonia, nitrites, and nitrates, and is converted into and forms part of numerous and most complicated substances, chiefly proteids. In the latter form it enters the animal economy, where the proteid breaks down into urea, uric acid, and other compounds, which rapidly decompose outside the organism and yield ammonia.

The bacteria mentioned above form an exception to this rule. On the roots of leguminosæ we may find small nodules, which are produced by an infection with certain bacteria, the two organisms, plant and bacteria, being symbiotic. If the leguminosæ are grown on a sterilized soil these nodules are not formed, and the plants attain only a slow and imperfect development, the amount of proteid formed in them being abnormally small. If however the soil be inoculated with the proper species of bacterium, the nodules soon make their appearance; the plants grow luxuriantly, and form large quantities of proteid out of the combined nitrogen of the soil.[1] It might have been expected that other microörganisms might have been found to possess the same properties. Up to the present, however, only one other species of bacterium, the Clostridium pasteurianum, has been found to possess the capacity of fixing free nitrogen.[2]

But in inorganic nature there must be factors at work which produce fixed nitrogen. Such a process has been recognized in atmospheric electrical discharges. It has been established by numerous experiments that, by means of electric discharges, nitrogen is united with oxygen to form nitric acid, and that, by sending electric sparks through a damp atmosphere, nitrogen and aqueous vapour combine to form nitrate of ammonia.[3]

$$2N + 2H_2O = NH_4NO_2$$

This process occurs on a large scale in every thunderstorm, the products being conveyed to the ground by the rain. Schönbein has pointed out a second process, viz., that wherever evaporation occurs, minute traces of nitrite of ammonia are formed in the air. The evaporation which is constantly going on from the surface of the plants themselves, may therefore be a source of combined nitrogen for them.

It follows that the whole store of fixed nitrogen is constantly increasing from various sources. Organic life would therefore develop with ever greater luxuriance were it not for the operation of other causes, by means of which combined nitrogen is again set free. This is effected by combustion. The burning up of vast forests of wood by man, which has been going on for thousands of years, detracts from the store of fixed nitrogen, to which animals and plants owe their existence; the total of life is no doubt diminished thereby, and the fertility of the soil must decrease. For this reason the project of cremation, recently introduced, should be abandoned, although the amount of fixed nitrogen destroyed in this manner would be much less than it is in consuming forests as fuel. Combined nitrogen is further destroyed by igniting gunpowder or other explosives, which are all derivatives of nitric acid. In this sense it may be affirmed that every shot from a fire-

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[1] W. O. Atwater and C. D. Woods, *Amer. Chem. Journ.*, vol. vi. p. 365, 1884 vol. xii. p. 256, 1890; vol. xiii. p. 42, 1891. H. Hellriegel and H. Willfarth "Unters. üb. d. Stickstoffnahrung d. Gramineen u. Leguminosen." Berlin, 1888. This discovery has been repeatedly confirmed by experiments of Beyerink, B. Frank, Bréal, Berthelot, Nobbe, and others.

[2] S. Winogradsky, *Arch. d. Sci. biol.*, St. Petersburg, vol. iii. p. 297, 1895.

[3] Berthelot, *Bull. Soc. Chim.* (2), t. xxvii. p. 338; *Ann. Chim. Phys.* (5), t. xii. p. 445, 1877.

arm kills, that it destroys life whether the ball strikes a living being or not. For no life is lost by the death of the individual; from the decay of the body equivalent new life arises. But the destruction of combined nitrogen means the definite diminution of the capital, upon the amount of which the total number of living beings depends.

These views of mine have been objected to on the grounds that certain bacteria have the power of fixing nitrogen, so that the burning of forests and dead bodies cannot be regarded as a spoliation of the capital of life. This is analogous to saying that a man may be robbed if he is going to inherit property. The formation and the destruction of fixed nitrogen are not mutually dependent processes. An increase in destruction does not imply an increase in formation, and the sum of life is therefore diminished. So long as there are fields where the ammonia of the soil is at a minimum, so long must the burning of plants and animals be regarded as a spoliation of living nature.

In the world about twenty men per thousand die every year, so that in fifty years the total number of deaths corresponds approximately to the total number of inhabitants on the globe, *i. e.*, about ten human beings to every square kilometer of land. (The total area of land on the earth's surface is 135 million square kilometers, and the total number of inhabitants about 1500 millions.) Thus if all dead bodies were burnt, they would amount in fifty years to ten per square kilometer, and in 5000 years to 1000 corpses. Can it be imagined that such a process would have no effect on the fertility of the soil? Adolf Meyer, in his "Text-book of Agricultural Chemistry" (part ii. p. 303, 1886), states that already it is no longer possible to obtain a proper yield from our cultivated lands without recourse to artificial manures containing combined nitrogen.

All the arguments which have been brought forward against burial are really only applicable to the interment of a number of bodies in a confined space, such as a churchyard, and have no weight against the only rational mode of disposal of the dead, viz., their distribution as widely as possible over the woods and fields. With all our improved means of communication this should be an easy task. The contamination of our water by dead bodies is negligible compared with that from sewage. It is absurd to cremate only the smaller part, and if we begin to destroy by combustion our excreta as well as our dead bodies, there will soon be a perceptible loss of fertility to the soil.

The remaining eight elements are derived by the plant from the soil. SULPHUR is widely distributed in inorganic nature as sulphates of the alkalies and alkaline earths. It enters the vegetable organism in this form, and takes part in the building up of the proteid molecule, in which it amounts to about 0.3 to 2 per cent. of the weight. It is chiefly taken up by the animal organism in the form of proteid, and is excreted for the most part in the highest oxidized condition as sulphuric acid, derived from the splitting up and oxidation of the proteid molecule. In this form, united with alkalies, it is again ready to repeat the cycle of life.

The course of PHOSPHORUS is very similar. It occurs in the inorganic world only in a high state of oxidation as phosphoric acid united with bases, especially with alkalies and alkaline earths, and enters the plant only in this form.

Although phosphoric acid is widely distributed over the whole surface of the globe, its amount in most soils is very small. As in the case of nitrogen, the quantity present in a field may be so little that vegetable life is unable to convert all the other elements into food. In rare cases this is also true of potassium; but there is never a lack of the remaining nutrient substance. In agriculture it is therefore of the greatest importance to determine which of these three elements is most deficient in any given soil. The fertility of the land will depend on the quantity of the substance of which there is a minimum. This is the important law which agricultural chemistry designates as the "Law of the Minimum." The element which is present in the smallest quantity must be supplied to the soil by artificial manuring. It is generally phosphoric acid; hence the use of bone-dust, apatite, and the like.

In the plant, phosphoric acid takes part in the formation of very complicated combinations—of the various forms of lecithin and nuclein, which are integral constituents of every vegetable and animal cell. It is chiefly in these combinations, and only to a small extent as salts, that phosphorus enters the animal body, which it leaves in the same form that it entered the plant—as a phosphate.

The circulation of CHLORIN is very simple; it occurs in nature only in the form of salts, chiefly united with sodium and potassium. In this form it enters and leaves the cycle of life. It takes no part in the formation of organic compounds.

The same is true of sodium, potassium, calcium, and magnesium. They occur in the inorganic world only as salts, enter plants as such, combine very loosely with organic matter, and are excreted from the animal body also in the form of salts.

Iron never occurs on the surface of the globe as a free metal, but chiefly in union with oxygen as ferrous and ferric oxides. The former is a strong base, and forms neutral salts with all acids. Ferric oxid is only a weak base, and is unable to fix carbonic acid. Ferrous silicates, when decomposed by atmospheric carbonic acid, yield ferrous carbonate, which is soluble in water containing carbonic acid, and is distributed by water all over the earth. But as soon as it comes in contact with the atmosphere, it is oxidized to ferric oxid, and the carbonic acid, being set free, is returned to the atmosphere. The ferric oxid, when it comes in contact with decomposing organic matter, is reduced, and ferrous carbonate is again formed and carried off by water, until it again comes in contact with air, and again aids in the oxidation of vegetable and animal refuse. Iron is therefore an indefatigable oxidizing agent. The iron prevents the retention of carbon in the soil, and enables it to return to the atmosphere, and thus to reënter the cycle of life.

The process of oxidation is rather more complicated when sulphur is present. Sulphur also acts as a carrier of oxygen. If decomposing organic substances meet simultaneously with oxids of iron and sulphates, *e. g.*, gypsum, not only is the oxygen of the oxids completely taken up, but that also of the sulphuric acid, sulphid of iron being formed. The latter, in the presence of air, may again be oxidized to sulphuric acid and ferric oxid, and then again act as an oxidizing agent. The sulphur required for the formation of sulphid of iron after the reduction of ferric oxid, may be yielded by decomposing organic matter itself, since this always contains proteid and consequently sulphur. In fact the organic sulphur compounds have themselves been formed in plants by the reduction of sulphates.

Iron plays the same part in our organism as it does in the earth's crust, the part of oxygen-carrier. Only the iron in our organism does not occur as ferric and ferrous oxids, but as a complex organic compound, the most complicated body which has hitherto been investigated with precision, and which contains at least seven hundred atoms of carbon in its molecule. This is the red coloring matter of the blood, hemoglobin, which, as oxy-hemoglobin, a loose compound with oxygen, corresponds to the ferric oxid, and, as reduced hemoglobin, to ferrous oxid. Hemoglobin also contains sulphur, and it may be that the sulphur of hemoglobin, and of all other proteid bodies, still retains its function as an oxidizing agent. At any rate, it cannot be to the iron alone that this property is due, since, as we shall see in the seventeenth lecture, the amount of loosely combined oxygen is much too large.

The enormous size of the hemoglobin molecule finds a teleological explanation if we consider that iron is eight times as heavy as water. A compound of iron which would float easily along with the blood-current through the vessels could only be secured by the iron being taken up by so large an organic molecule.

Hemoglobin first makes its appearance in the animal organism. It does not exist in plants. The plant has the power of assimilating inorganic compounds of iron, and of using them for building up complex organic compounds, which have not yet been sufficiently investigated. From these bodies the hemoglobin is produced in the animal economy (*vide* Lecture XXV.).

Iron likewise plays an important part in vegetable life;[1] we know that chlorophyl granules cannot be formed without it. If plants are allowed to grow in nutritive solutions free from iron, the leaves are colorless, but become green as soon as an iron salt is added to the fluid in which the roots are immersed. It is even sufficient merely to brush the surface of the colorless leaf with a solution of an iron salt to cause the appearance of the green color in the part thus painted. Chlorophyl itself contains no iron, and we do not know in what way the iron is concerned in its production. It seems however that there is a proportionality between the amount of iron and that of chlorophyl in any given part of the plant. Thus Boussingault[2] found .0039 per cent. Fe in the green leaves of a cabbage, while the inner etiolated leaves contained only 0.0009 per cent. Fe.

It is not yet known in what form and by what path iron leaves the animal body. Urine contains scarcely perceptible traces of iron, probably as an organic compound. The feces always contain a considerable quantity of sulphid of iron. But it cannot be determined how much of this is derived from the food, and how much from the digestive secretions. Outside the body, the sulphid of iron is converted by the atmospheric oxygen into sulphuric acid and oxid of iron, and the cycle is complete.

In addition to the twelve elements alluded to, the following elements are met with in certain organisms, though they

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[1] Molisch ("Die Pflanze in ihren Beziehungen zum Eisen") gives an account of the botanical literature on the relations of iron in plants.

[2] Boussingault, *Compt. rend.*, vol. lxxiv. p. 1356: 1872; E. Häusermann, *Zeitschr. f. physiolog. Chem.*, vol. xxiii. p. 587: 1897.

are not always an integral part of their composition: silicon, fluorin, bromin, iodin, aluminium, manganese, and copper.

SILICON does not occur in the free state, but only as silicic acid. This compound, as already mentioned, is amongst the most widely distributed bodies in the earth's crust. The alkaline salts of silicic acid are soluble in water, and the free acid, when liberated by carbonic acid from certain silicates, at first appears as a hydrated acid apparently in a state of solution, in what is known as a colloid condition (see Lecture IV.). Probably plants absorb silicic acid in both these forms. All the higher plants seem to contain silicic acid. Among cryptogamic plants, the reeds and grasses are distinguished by the large amount of silicic acid they contain. Certain unicellular algæ (the Diatomaceæ) cover themselves with a shell of silica. Silicic acid is said to be absent from the ash of certain fungi.

But it would not appear that silicic acid plays any important part in the economy of the higher plants. This is shown by the following experiments on the graminaceæ, which are rich in silicon, as wheat, oats, maize, barley. When these plants are allowed to germinate in nutrient fluids free from silica, so that they can only obtain mere traces of silicic acid from the glass vessel containing the solution, they develop completely, and pass through a perfectly normal course of life. In the ash of maize grown in this way, only 0.7 per cent. of silicic acid was found, whilst, under ordinary conditions of growth, 20 per cent. is the average quantity.[1]

Whether silicon exists in plants only as silicic acid, or whether it forms more complex compounds, has not been ascertained. Silicon is a tetravalent element, like carbon. Silicic acid is quite analogous in its composition to carbonic acid. Hence a probability that silicon could form numerous compounds which would bear the same relation to silicic acid as the organic compounds do to carbonic acid; and, as a matter of fact, Friedel and Ladenburg[2] have succeeded in preparing a series of such compounds. But their existence in plants has, up to the present time, not been detected.[3]

Silicic acid is taken up by animals in the form of vegetable food. It is absorbed by the alimentary canal, and passes through all the tissues; hence minute traces can be demon-

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[1] Sachs, "Flora," p. 52: 1862; and *Wochenblatt der Annalen der Landwirthschaft*, p. 184: 1862.

[2] C. Friedel and A. Ladenburg, *Compt. rend.*, vol. lxvi. p. 816: 1868; and vol. lxviii. p. 920: 1869. *Ber. d. deutsch. chem. Ges.*, p. 901: 1871; and pp. 319, 1081: 1872.

[3] Ladenburg, *Ber. d. deutsch. chem. Ges.*, vol. v. p. 568: 1872; W. Lange, *ibid.*, vol. xi. p. 822: 1878.

strated in every organ. It is contained in considerable quantity in the urine of herbivorous animals, and in sheep sometimes occasions stone in the bladder. It appears however to be of importance only in the development of hairs and feathers,[1] the ash of which is always rich in silicic acid. The constant presence of silicic acid in eggs points to its being essential in the development of birds.

FLUORIN has been found in very small quantity in some plants and animals. It is difficult to detect,[2] and it may possibly be more widely existent in organic nature than has been suspected. It is invariably found in the bones and teeth of men and mammals, although we have not yet succeeded in ascertaining the exact amount by our present methods. It is also said to have been detected in the blood of mammals and of birds.[3] Recently, G. Tammann,[4] by means of careful determinations, has found .001 per cent. fluorin in the yolk of eggs, .0007 per cent. in calves' brains, and .0003 grms. in one liter of cow's milk. In 3000 ccm. of cow's blood, the presence of fluorin could be qualitatively detected. Small quantities of fluorin are distributed everywhere in the earth, in the form of fluorspar and apatite; therefore plants are never without it. It acts perhaps differently in the nutrition of men and animals. It would be very interesting to have the exact amount of fluorin in our food determined, and also the quantity we really need of it. At any rate, the above-mentioned "law of the minimum" holds good for animal as well as for vegetable growth. It is conceivable that milk, although rich in the most important substances of nutrition, might yet be useless for the growth of the infant, for want of the necessary trace of fluorin.

BROMIN and IODIN are present in many kinds of seaweed, and thus pass into the system of marine animals. A collected account of the organisms containing iodin, which have been utilized for therapeutic purposes, has recently been published by E. Harnack.[5] The horny axial skeleton of a

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[1] [It is interesting to note that Drechsel, in his last published paper, has described an organic silicon compound, viz., a cholesterin ester of silicic acid, as occurring in birds' feathers. This is the first organic silicon compound which has, so far, been found to occur in nature. *Centralbl. f. Physiol.*, vol. xi. pp. 361–363: 1897.]

[2] See G. Tammann, *Zeitschr. f. analyt. Chem.*, vol. xxiv. p. 328: 1885, where an account of the literature on the methods of detecting fluorin will also be found.

[3] G. Wilson, *Trans. of the Brit. Ass. for the Adv. of Sci.*, p. 67: 1851; and J. Niclès, *Compt. rend.*, vol. xliii. p. 885: 1856.

[4] G. Tammann, *Zeitschr. f. physiol. Chem.*, vol. xii. p. 322: 1888.

[5] E. Harnack, *Münch. med. Wochenschr.*, No. 9: 1896.

species of coral (*Gorgonia*[1]) is rich in iodin, part of which at any rate is in organic combination. Iodin is however also contained in small quantities in many land plants as well as in fresh-water animals, such as the fresh-water sponges (*Spongia fluviatilis*).

Universal attention has recently been attracted by Baumann's discovery of iodin in the thyroid gland of men, sheep, pig, and apparently many other mammals.[2] Further investigations have shown that iodin is also contained in the thymus,[3] the spleen, and the pituitary body of man,[4] and in the ovaries[5] of the cow and pig. In all the animal and vegetable organisms just mentioned, the iodin is present for the greater part as an organic compound, although only the iodin compound of Gorgonia has been hitherto isolated as a chemical individual in a crystalline form.[6] This compound is an acid of the composition $C_4H_8NIO_2$. Drechsel suggests that it is an amido-iodobutyric acid, and has proposed to call it, for the present, iodogorgonic acid.

We know absolutely nothing as to the significance of iodin for any vital functions.

Aluminium is one of the elements most frequently met with. Its sesquioxide, alumina, is found, united with silicic acid, in almost all crystalline rocks which form the larger portion of the great mountain ranges. Mixed with the products of disintegration of these rocks it is found everywhere in ample quantity in the soil. It is therefore very remarkable that alumina takes little or no part in the metabolism of living beings. It has been shown positively to exist in any noticeable quantity only in a few plants, especially in a few kinds of lycopodium, in the ash of which it amounts to over 57 per cent. We do not know whether it is essential for these plants, nor of what use it is to them; no experiments have yet been made to decide this question. Alumina has not yet been detected in the animal body.

Manganese is found in considerable quantity in the ash of a few plants, although nothing is known concerning its significance in vital processes. Traces of this metal are found all through the vegetable kingdom, and occasionally in the animal body.

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[1] E. Drechsel, *Centralbl. f. Physiol.*, vol. ix. p. 704; 1895; and *Zeitschr. f. Biolog.*, vol. xxxiii, p. 96: 1896.

[2] Compare Lecture XXIX.

[3] Baumann, *Münch. med. Wochenschr.*, No. 14: 1896.

[4] Schnitzler u. Ewald, *Wien. klin. Wochenschr.*, No. 29: 1896.

[5] Schaerges, *Pharm. Zeitg.*, No. 71: 1896; and E. Barell, *idem*, No. 15: 1897.

[6] Drechsel, *loc. cit.*

Minute traces of most of the other metals are occasionally found in plants and animals. They should not on that account be considered as essential constituents.

The presence of COPPER in the blood of certain cephalopods and crustacea is noteworthy. This metal appears to be present in the form of an organic compound, and to serve as oxygen-carrier, thus playing a part similar to that of the iron in hemoglobin. The blood of these animals is blue, but loses its color as soon as the oxygen is withdrawn either by pumping, by the passage of a stream of an indifferent gas, or by the action of reducing agents. When shaken up with air the blood again becomes blue. The latest experiments on this subject have been carried out by Frédéricq,[1] whose essay also contains an account of the work done by his predecessors.

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[1] Léon Frédéricq, *Bulletins de l'ac. roy. de Belgique*, sér. ii. t. xlvi. No. 11: 1878; *Compt. rend.*, t. lxxxvii. p. 996: 1878.

LECTURE III

CONSERVATION OF ENERGY.[1]

MOST intimately connected with the circulation of the elements is the circulation of energy. The latter is not however limited to this earth; it streams on to our planet with the sunlight, and, having run its course through plant and animal life, streams back again into illimitable space.

It is as impossible to destroy energy as matter. Energy itself cannot be directly observed and pursued. We can say nothing more definite about it than that it is the cause of motion. But we can prove that motion is never annihilated, for whenever motion ceases, its cessation is only apparent. The movement of masses of matter, visible to us, has either changed into a movement of the smallest particles of matter, of the atoms, or into 'latent motion,' into so-called 'potential energy,' from which, at any time under appropriate conditions, the same amount of motion can again arise.

If a stone fall to the ground and remain lying there, motion has not ceased. The place on the ground where it fell, and the stone itself, have become warmed, and heat is well known to be a mode of motion. If a stone is thrown straight up in the air, it rises with decreasing rapidity and comes at last to rest. At that moment its movement is latent, and is stored up in it as potential energy. By virtue of this potential energy it now comes down again, and reaches the ground at the same velocity with which its ascent began. In rising, the energy of movement, the so-called 'kinetic energy,' is converted into potential energy; in falling, the potential into kinetic energy. The conversion of kinetic into potential energy is called 'work,' and the science of mechanics teaches the well-known fact that work is measured by the product of the weight raised into the height to which it is raised, and that it is always the same as the kinetic energy,

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[1] Physiology cannot be studied to any advantage without a thorough knowledge of the law of the conservation of energy, which can only be acquired by advanced mathematical and physical studies. This lecture may serve the beginner, who has hitherto neglected these subjects, as a slight preliminary account.

which is measured by the product of half the mass into the square of the velocity. If the stone that is thrown up be supported at the moment it has reached the highest point and comes to rest, the energy can remain stored up in it for an unlimited period. But as soon as the support is removed, potential is again converted into kinetic energy; it falls with increasing rapidity, and reaches the ground at the same speed with which its ascent began. Hence none of the kinetic energy has been lost. If it strikes the ground, an amount of heat is generated, which under appropriate conditions—for instance, by means of a steam-engine—would exactly suffice to raise the stone to the same height from which it fell. Thus no energy is lost in the conversion of the kinetic energy of moving masses into the kinetic energy of moving atoms, and *vice versâ*. As is well known, it has been proved by numerous experiments, made by different observers and conducted upon various methods, that 425 kilogrammeters of work produce one unit of heat (*i. e.*, the amount of heat required to raise the temperature of one kilogramme of water by 1° C.), and that the unit of heat exactly suffices to accomplish work equal to 425 kilogrammeters.

Let us imagine a tube to be laid through the globe and its center of gravity, from us to our antipodes, and let us further imagine a stone brought to rest in this tube, so that the center of gravity of the stone coincides with the center of gravity of the earth; in this case the stone would remain motionless and free, suspended in the air. But if the stone, by virtue of any kinetic energy, were raised to our end of the tube, a reserve of potential energy would now be stored up in it, by means of which the stone, as soon as it is left to itself, returns with increasing rapidity to the middle of the tube. At the moment when its center of gravity coincides with that of the earth, all potential energy is used up and converted into kinetic energy, and has attained its greatest velocity. This kinetic energy cannot be lost; it drives the stone further on, it is reconverted into potential energy, work is accomplished, the stone is driven to the other end of the tube, to the antipodes. By this time the kinetic energy is used up, and is contained in the stone as potential energy, by means of which the stone again falls with increasing speed to the earth's center of gravity, and rises with diminishing velocity to us. And if the tube be free from air, the stone must thus swing backwards and forwards to all eternity, none of its movement being lost. But if there is air in the tube, a part of the kinetic energy of the stone will be continually given over to the individual molecules of air; the stone will swing backwards and forwards at constantly decreasing distances from the center of gravity, where it finally comes to rest. At this moment, the whole kinetic energy of the stone's moving bulk is converted into the kinetic energy of moving molecules, which we call heat. But nothing is lost; precisely as many units of heat are produced as correspond to the kilogrammeters of work performed by the rise of the stone from the earth's center of gravity to the end of the tube.

The same principle seen in this imaginary and impracticable experiment may be observed, only in a more complicated form, in every swinging pendulum. The pendulum would also oscillate to all eternity, if the kinetic energy of the moving mass were not converted into heat by the friction at the point of attachment and with the air.

If we make use of that form of kinetic energy which we call the electric current, to split up a chemical compound (for instance, to resolve water into its elements, hydrogen and oxygen), a part of the kinetic energy disappears, but only apparently so; it is converted into that form of latent movement which we term chemical potential energy, and which is entirely analogous to the force with which the stone falls when raised. Chemical potential energy is stored up in the separate atoms. If they again unite, the potential energy they contain is again converted into kinetic energy, which appears to us as light and heat; as, for instance, when a flame is produced by the combination of oxygen and hydrogen. By means of a thermopile, the heat produced might be reconverted into electrical movement, which would be found exactly equal to the amount originally required to split up the water. Nothing would be lost.

We thus see that nature possesses a certain store of kinetic energy, which can in no way be either increased or diminished. If one part of matter comes to rest, another part is set in motion. Movement of masses is converted into movement of molecules, molecular movement into movement of masses; kinetic into potential energy, and potential into kinetic energy. The sum total of all potential energy and of all kinetic energy always remains the same. This law is called the Law of the Conservation of Energy.

All movements on the surface of the earth (with the single exception of the tides, which are connected with the rotation of the earth on its axis) may be traced back to one common source, to the sun's rays of light and heat. The varying degree of heat of the different layers in air and water is the cause of all currents of sea and air, the storms and winds. Sailing vessels and windmills are moved by sunbeams. By using up the kinetic energy of the sun's heat, vapor arises from the surface of water, and is raised to the higher layers of the atmosphere. If the vapor is condensed in the colder upper regions, the kinetic energy of the waves of ether reappears as the kinetic energy of the falling raindrops, or, when the raindrops collect, as the kinetic energy of flowing brooks and rivers. It is sunlight that reappears in the sparks from the millstone; it is the sun's heat which issues from the glowing hammers and saws, wheels, axles, and rollers of all machines set in motion by water.

We now come to the question of the forms of energy and motion which are met with in vital processes. We have seen that the plant is always taking up carbonic acid and water, separating the oxygen from these compounds, and thereby forming other compounds poorer in oxygen and with a great affinity for oxygen. There is thus a large reserve of chemical potential energy stored up in the plant. By combustion of the plant by reunion of its constituents with oxygen, we can convert this potential energy into heat, and the heat, by means of steam engines, into mechanical work. Now, what is the source of this chemical potential energy? It cannot have originated from nothing. Energy is eternal. But no potential energy is conveyed to the plant by its food. Carbonic acid and water are fully oxidized compounds; they cannot produce movement, any more than the stone lying on the ground. Not till the stone is raised by the employment of kinetic energy, can it fall down; and not till the oxygen is separated from the carbon and hydrogen in the plant by the employment of kinetic energy, can chemical potential energy arise in it, to be converted into light and heat and mechanical work. The force which effects the separation of the oxygen in the plant is again nothing but sunlight. We know that the plant liberates oxygen only so long as sunshine reaches it, and that the amount of oxygen set free varies in proportion to the intensity of the light. This maintenance of the proportion was proved by Wolkoff[1] by the following simple experiment.

Wolkoff counted the gas-bubbles which arose from water-plants when the rays of the sun, conducted through a flat piece of ground glass, were allowed to fall upon them. The water-plants were in a glass vessel, which could be moved to any distance from the light as required. The intensity of the light is well known to be in inverse proportion to the square of the distance from the point of light. Wolkoff found that the

[1] Al. von Wolkoff, *Jahrb. f. wissensch. Botanik.*, vol. v. p. 1: 1866.

number of oxygen-bubbles was increased and diminished in simple proportion to the intensity of the light.

Van Tieghem[1] obtained the same result when he tried the experiment with artificial light. The number of gas-bubbles from the water-plants diminished as the square of the distance from the candle.

Hence there can be no doubt that all the potential energy of vegetable substances is converted sunlight. It is sunlight that reappears in the fire of burning wood. It is sunlight that gives us light in the form of gas-jets and petroleum flames. The gaslight which at this moment illuminates us, has shone on our earth before, millions and millions of years ago; it has lain dormant in our earth for millions of years, and reappears again at this moment. The whole immense store of energy which lies in the vast coal strata, which sets all machines and locomotives in motion, is only the fixed kinetic energy of sunlight which was once shining upon the luxuriant vegetation of the prehistoric world.

The substances formed by plants serve as food for animals. The oxygen which is liberated from the water and carbonic acid in the plant by the kinetic energy of sunlight, is in the animal body again united with compounds that are deficient in oxygen, and the ultimate products of this combination are again given off as carbonic acid and water, the same simple substances which serve the plant as food. The chemical potential energy of food is thus used up. But, as no energy can perish, we must expect to find an equivalent amount of other forms of energy appearing in the animal body. And indeed we know that, firstly, all animals have a temperature higher than that of their surroundings, that they are thus continually producing heat; and that, secondly, they carry out movements, or perform work.

The sum of the work executed by an animal, and of the heat which it gives out, must therefore be exactly equivalent to the chemical potential energy taken in with its food, and to the kinetic energy of sunlight used up in the production of this potential energy in the plant.

The difficulties of obtaining precise experimental proof of this equivalence are very great. So far as the precision hitherto attained allows us to judge, direct experiments prove that such equivalence does exist: that the amount of heat and work produced by an animal, expressed in units of heat, is equal to the amount of heat generated by the food-stuff of the animal when burnt outside the organism.

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[1] Van Tieghem, *Compt. rend.*, vol. lxix. p. 482: 1869.

The first experiment of this kind was carried out by Lavoisier[1] as early as the year 1780. The object was to prove that combustion is the sole source of animal heat. A guinea-pig was placed in an ice-calorimeter, and the quantity of water produced in ten hours by the melting of the ice was measured. It amounted to 341.08 grms. The same guinea-pig was then put under a bell-jar over mercury. A current of air was passed through the bell-jar and then conducted through caustic potash, which retained the carbonic acid. The amount of the latter was quantitatively determined. The mean of several experiments showed that the guinea-pig in ten hours gave out 3.333 grms. of carbon in the form of carbonic acid. Lavoisier and Laplace had previously, by means of the calorimeter, determined the heat of combustion of carbon, and found that the heat produced by the combustion of 3.333 grms. of carbon melted 326.75 grms. of ice. Were Lavoisier's hypothesis, that animal-heat arises from the combustion of the carbon in the food-stuffs, correct, the amount of heat or of ice-water found in the above experiment on an animal would necessarily be precisely as great as in the combustion of the carbon, provided the production of carbonic acid were the same in both instances. As a matter of fact, it was found thus—

$$\frac{326.75}{341.08} = 0.96.$$

It was a mere chance that the numbers approximated each other so closely. Any one with our present knowledge, who criticised the experiment, would easily discover numerous sources of error. Indeed its chief defects did not escape Lavoisier's penetration. He had already discovered that the whole of the oxygen inspired did not reappear in the carbonic acid exhaled, and he therefore assumed that the oxygen which had disappeared went to form water. Lavoisier had further observed that the temperature of the animal in the calorimeter was lower at the conclusion of the experiment than at the commencement; that the animal therefore, during the progress of the experiment, partially lost its heat, which arose from combustion that took place before the experiment began, and which did not therefore correspond to the amount of carbonic acid exhaled during the experiment. For both reasons, the quantity of water produced in the calorimeter must be greater than what would correspond to the carbonic acid produced.

The necessity for a more exact repetition of Lavoisier's

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[1] Lavoisier et de la Place, *Mémoires de l'Acad. royale des Sciences*, p. 355: 1780.

experiments was soon afterwards recognized by the French Academy; and in 1822 they offered a prize on the subject of the source of animal heat. There were two competitors, Despretz and Dulong. The prize was awarded to Despretz and his work appeared in the year 1824.[1] Dulong's work, which was carried out on the same principle, was not printed till after his death.[2]

Both experimenters made use of a water-calorimeter. The animal being in the calorimeter, atmospheric air was passed from one gasometer through the air chamber immediately around the animal, and collected in another gasometer. In this way the quantity of the oxygen used up, and carbonic acid formed, was determined. The latter did not correspond to all the oxygen consumed; the excess of oxygen was supposed to have united with hydrogen to form water. The heat of combustion of hydrogen and carbon was calculated from the figures given by Lavoisier and Laplace. The amount of heat estimated in this way was compared with the amount of heat produced in the calorimeter. Both Despretz and Dulong found the amount of the former smaller than of the latter. In the experiments of Dulong, the number calculated amounted from 68.8 to 83.3 per cent. of the number found; in those of Despretz, from 74.0 to 90.4 per cent.

Among the numerous sources of error in this calculation, the following may be specially noticed: 1. The numbers given by Lavoisier and Laplace, which form the basis of the comparison, are, as subsequent and more exact investigation has shown, too low. 2. The heat of combustion of the food-stuffs is not equivalent to that of their component elements, but a little less, since a certain amount of kinetic energy is used up in effecting their dissociation. 3. The quantity of carbonic acid in the expired air must be too small, since the gas in the gasometer was confined over water, which would absorb some of the carbonic acid. 4. The time occupied by the experiment was much too short; it was only two hours. The processes of combustion and the taking up of oxygen or elimination of carbonic acid are not proportional in every short interval; only during longer periods is there an approximate correspondence. The quantities of oxygen and carbonic acid, and of the intermediate products of combustion contained in the tissues of the body, vary greatly at different times.

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[1] Despretz, "Recherches expérimentales sur les causes de la chaleur animale": Paris, 1824; also *Ann. de chim. et de phys.*, vol. xxvi. p. 337: 1824.

[2] Dulong, "Mémoire sur la chaleur animale," *Ann. de chim. et de phys.*, sér. iii. vol. i. p. 440: 1841. See also "Recherches sur la chaleur, trouvées dans les papiers de M. Dulong," *Ann. de chim. et de phys.*, sér. iii. vol. viii. p. 180: 1843.

At a later period Gavarret[1] calculated the numbers obtained by Dulong and Despretz, and, by correcting certain errors, found the values 84.7 to 101.8 per cent., as a mean 92.3 per cent.; instead of the proportion of 74.0 to 90.4 per cent., as found by Dulong and Despretz.

The movements of the animal while confined in the calorimeter must have been almost entirely converted into heat and observed as such; they must have produced heat by the mutual friction of the parts moved, by the rubbing of the animal against the walls of its cage, and by the shaking of the water in the calorimeter thus set up.

In recent years M. Rubner[2] has taken up the same subject with all the aids afforded by modern apparatus and technique, and has succeeded in demonstrating the exact equivalents between the chemical potential energy taken up by the body in the form of food and the kinetic energy given out by the animal. In Rubner's experiments on dogs these amounts, as a matter of fact, differed only by about $\frac{1}{2}$ to $1\frac{1}{2}$ per cent.

We thus see that the law of the conservation of energy rules in the department of animal life. The body-heat, our movements, all our vital functions—so far as they are perceptible to our senses—are transmuted sunlight.

We may now inquire into the relation borne by our psychical processes to the conservation of energy. Are all our feelings, emotions, instincts, ideas only converted sunlight, or must we assume that the world of the internal sense does not obey the great uniform law to which the whole world of the external senses yields constant and unwavering allegiance?

It is beyond doubt that there is a certain causal connection between psychical processes and certain material modes of motion in our bodies. Sensation is excited by a process of movement in the nervous system. A muscular contraction is the result of an impulse of the will. But the question arises as to the nature of this causal connection. Is it really a causal connection of the same kind as the law of the conservation of energy demands, that proportion should exist between cause and effect? Or have we to deal with other kinds of causal connection?

Above all things, we must sharply distinguish between an immediate cause and an ultimate cause, a distinction so necessary for the comprehension of physiological processes that I may be permitted to give one or two illustrations. It is usual to define the cutting through of a string by which a weight is held up as the cause of falling. But the real cause is the

[1] Gavarret, "De la chaleur produite par les êtres vivants": 1855.

[2] M. Rubner, *Zeitschr. f. Biol.*, vol. xxx. p. 73: 1894.

work which has been performed in raising the weight. This is proportional to the kinetic energy of the falling weight. If the lifting is effected by muscular force, the latter owes its origin to the chemical potential energy of food, which was originally derived from the kinetic energy of sunlight in the plant. If the falling weight strikes the ground, the energy of sunlight again makes its appearance as heat. All these forces, the kinetic energy of the sunlight, the chemical potential energy of food, the kinetic energy of muscular movement, the potential energy of the lifted weight, the heat produced by the falling weight, &c., are related as cause and effect; they are proportional and equivalent—the same thing appearing in different shapes. The effect is the cause itself in a changed form. Cutting the string is only the immediate or exciting cause, the impetus which starts the conversion of cause into effect, of potential into kinetic energy. Between the exciting cause or 'liberating force,' as it is also called, and the effect, there is no sort of proportion. The weight may be hung up by a string and the latter cut through with a razor, or the same weight may be hung up by a rope and the latter shot through by a cannon-ball—the kinetic energy of the falling stone remains the same.

The movement of a locomotive is transmuted heat; the heat is produced by chemical potential energy, by the affinity of the fuel for oxygen; the chemical potential energy is the converted energy of sunlight. The kinetic energy of the moving engine is completely used up in overcoming friction. The heat which causes the movement of the locomotive appears again in the heated rails, wheels, and axles. It is the same heat which, as the heat of the sun, produced the chemical potential energy in the plant. The energy of the sunlight, the potential energy of the fuel, the heat of the furnace, the kinetic energy of the engine, the heat produced by friction, are all proportional and equivalent; they are identical. The flame, which was used to light the fire in the furnace, is merely the exciting cause of the conversion of chemical energy into heat; the amount of heat produced is totally independent of it. A single lucifer match may set fire to one pound or a thousand pounds of wood, or even to a whole forest; but the heat produced is in proportion to the amount of chemical energy used up, and is entirely independent of the liberating force.

In the case of a rifle, the pulling of the trigger constitutes the liberating force for converting the potential energy of the spring into the kinetic energy of the falling hammer. The energy of the hammer is converted into molecular movement, which again acts as a liberating force in causing the explosion of the percussion-cap; this explosion acts as the exciting cause for the conversion of the chemical potential energy of the powder into the kinetic energy of the ball.

In addition to the ultimate cause, and the exciting cause, a third factor is generally required in the production of a definite result, which I will call the determining factor. In the last illustration, the determining factor for the projection of the bullet is to be found in the fact that the latter is contained in the barrel of the rifle, and thus only able to pass in one direction. For the production of a definite movement, a certain arrangement of surrounding objects is a necessary determining factor. We can thus distinguish between three sorts of causes: the ultimate cause, the exciting cause, and the determining cause.

It must be observed that in certain exceptional cases there is a proportion between the effect and the exciting cause. A well-known instance of this is seen in the drawing up of a sluice. The work performed in raising it is in proportion to the cross section of the falling current of water, and to the kinetic energy of the water. Nevertheless, the drawing up of the sluice is only the exciting cause which converts the potential energy of the dammed up water into the kinetic energy of water in motion.

Similarly, if we have a number of weights hung up by strings of uniform size, the work done in cutting through the strings will be in proportion to their number, and consequently in proportion to the kinetic energy of the falling weights. And yet the cutting is only the exciting cause.

We may now return to the question as to the relation between psychical and physical processes.

The impulse of the will and muscular contraction certainly do not stand to each other in the relation of cause and effect in the limited sense. The impulse of the will is merely the exciting cause. The ultimate cause is the chemical potential energy of the food which is used up in the muscle, and is therefore converted sunlight. But the impulse of the will does not even afford the direct impetus for the conversion of chemical energy into the kinetic energy of muscle. There is probably a long chain of causes, such as processes in the brain, nervous system, and muscle, analogous to those shown to exist in the illustration of the rifle.

The question as to the nature of the causal connection between stimulation of the senses and the sensations themselves, is much more difficult to decide. Here there is undoubtedly quantitative proportion. The intensity of the sensation increases with the strength of the stimulation; but is there any proportionate relation between the two?

We shall not be able to decide this question, so long as we possess no means of measuring the intensity of sensations, or of any other psychical conditions and processes; in the present state of human knowledge and of human intellect, it appears quite inconceivable that such means should ever be discovered.[1] We are therefore unable to answer the question whether the phenomena of consciousness follow the law of the conservation of energy, and whether they are transmuted sunlight.

I must note that there is probably, in the afferent and central organs, a chain of processes intervening between stimulation and sensations, as there is between will and muscular action. We are quite unable to decide whether the last form of motion, which reaches the brain as the result of stimulation, is converted into sensation, or only serves as an impulse originating sensation, possibly from chemical potential energy. It is conceivable that an entirely new and particular kind of causal connection may be at work in this case.

The theory has nevertheless often been advanced that there is an exhaustion of chemical potential energy, of food-substances, corresponding to the performance of psychical functions. People have even tried to prove experimentally that intellectual exertion has an influence on metabolism, as shown by the amount of excretions. All these experiments fail on account of the impossibility of measuring intellectual exertion, of even deciding whether it was greater or less. A man who shuts himself up in a dark room, with the intention of keeping his mind a blank, may involuntarily exercise it more than if he were to sit down to his books with the intention of exerting all his intellectual faculties; besides, we ought to take into consideration the emotions, which probably far exceed all mental exertions in the expenditure of energy, and which we cannot call into play or dismiss at will.

We must consider moreover that the weight of the brain is less than 2 per cent. of the weight of the body, and that only a portion of the brain is employed in mental functions. Even if the metabolism of this organ were, by higher psychical

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[1] Fechner ("Elemente der Psychophysik": Leipzig, 1860), taking Weber's law as his starting-point (viz., that the increase of stimulation must grow in proportion to the stimulation already existing, in order to produce a minimal increase in sensation), arrives at the conclusion that sensations are proportionate to the logarithm of the stimuli. Attention has frequently been drawn to the fact that the assumed equality of the minimal increments of sensation, upon which the computation is founded, is purely arbitrary. This is not the place to enter more fully into this subject.

activity, promoted to the utmost, we could not expect to recognize this fact in an increase of the total metabolism. Even if it could be distinguished, we should not be justified in concluding that the work of the mind was converted potential energy. The connection might be an indirect one.

With a knowledge of this point of view, the beginner will be in a position to peruse critically the works[1] that have appeared concerning the influence of mental work on metabolism.

In recapitulating the main features of our previous remarks the following contrasts strike us in the changes that animal and vegetable substances undergo:—

1. The plant forms organic substances; the animal destroys organic substances. The vital process in the plant is synthetic, in the animal analytic.

2. The life of the plant is a process of reduction; the life of the animal a process of oxidation.

3. The plant uses up kinetic energy and produces potential energy; the animal uses up potential energy and produces kinetic energy.

But "nature takes no leaps." In morphology no definite demarcation can be drawn between plants and animals; in the same way the contrast between them disappears when we examine the two kingdoms in relation to the conversion of energy and metabolic processes which they exhibit.

There are unicellular beings without chlorophyl, such as fungi and bacteria, which are incapable of assimilating the carbon of carbonic acid. It must be brought to them as an organic compound, as sugar, tartaric acid, &c. Here they resemble animals. But they can assimilate nitrogen in inorganic compounds, as ammonia and nitric acid; here they resemble plants. The fungi and bacteria, which cause fermentation and processes of decomposition (see Lecture XI.), use up chemical potential energy and develop kinetic energy, heat, and movement; again behaving like animals. But by synthesis they form proteid from ammonia and sugar, thus again behaving like plants. In our future observations we shall see that in every cell, even of the most highly organized animal, synthetic processes occur side by side with processes of decomposition, as they do in the cells of plants. Within the rigid cellulose-wall of every vegetable cell is a contractile protoplasmic body which

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[1] Bœcker, *Beitr. z. Heilkunde:* 1849; Hammond, *Amer. Journal of Medical Sciences*, p. 330: 1856; Sam. Haughton, *Dublin Quarterly Journal of Medical Science*, p. 1: 1860; J. W. Paton, *Journal of Anatomy and Physiol.*, vol. v. p. 296: 1871; Liebermeister, *Handb. d. Pathol. u. Therap. des Fiebers*, p. 196: Leipzig, 1875; Speck, *Arch. f. exper. Path. u. Pharm.*, vol. xv. p. 81: 1882.

breathes and performs 'active' movements like every animal. In every part of a plant oxygen is used up and carbonic acid produced, as in every animal; only that, in the parts of the plant which have chlorophyl, this process of oxidation is hidden by the more powerful process of reduction. But even this only takes place so long as sunlight shines upon those particular parts. In the dark, the parts of the plant containing chlorophyl breathe like animals; the parts without chlorophyl do so in the sunlight as well.

The contrast disappears however still more completely in certain highly organized phanerogams, so-called parasites, which do not possess chlorophyl, and which derive their nourishment from the organic substances formed by other plants. The Monotropa, for instance, is in morphological structure a Pyrolacea, but in its metabolism it is an animal.

On the other hand, there are animals which contain chlorophyl. Certain worms (Planariæ) and Celenteratæ (*Hydra viridis*) have chlorophyl-granules, seek sunlight, and give off oxygen in the light, but soon die if kept in the dark.[1] It has however been more recently shown by Géza Entz[2] and Karl Brandt[3] that the chlorophyl-granules are not free in the tissues of the above-mentioned animals, but are enclosed in unicellular algæ, which live in these animals as 'symbionta.'[4] But the chlorophyl-granules in plants may be likewise only symbionta. So far it is certain that they never arise in the tissues of plants in any other way than by division of other chlorophyl-granules already there.[5] Besides this, Engelmann[6] has shown that

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[1] P. Geddes, *Compt. rend.*, vol. lxxxvii. p. 1095: 1878; and *Proc. Roy. Soc.*, vol. xxviii. p. 449: 1879.

[2] Géza Entz, Ueber die Natur der 'Chlorophyllkörperchen' niederer Thiere, *Biolog. Centralblatt*, vol. i. No. 21, p. 646: January 20, 1882.

[3] Karl Brandt, *Verh. d. physiol. Gesellsch.:* Berlin, November 11, 1881; *Biolog. Centralblatt*, vol. i. No. 17, p. 524; *Arch. f. Anat. u. Physiol.*, p. 125: 1882; *Mittheilungen a. d. zoolog. Station zu Neapel.*, vol. iv. p. 191: 1883.

[4] The term 'symbionta' is applied to those parasites which do no harm to their hosts, each being of mutual assistance to the other. A known instance of symbiosis occurs in the relationship between algæ and fungi in the thallus of herpes (*Flechtea thallus*), discovered by Schwendener (Nägeli's *Beitr. z. wissensch. Bot.*, Heft ii., iii., and iv.: Leipzig, 1860–68). The more recent discovery of numerous examples of symbiosis is undoubtedly an acquisition of the greatest importance in every branch of physiology. The name "Symbiosis" was introduced by De Bary, "Die Erscheinung der Symbiose," Vortrag, Strasbourg: Trübner, 1879. An interesting account of the literature of this subject will be found in O. Hertwig's "Die Symbiose oder das Genossenschaftsleben im Thierreich," Vortrag: Jena, 1883.

[5] Arthur Meyer, "Das Chlorophyllkorn," p. 55: Leipzig, 1883; A. F. W. Schimper, *Jahrbücher für wissensch. Botanik*, vol. vi. p. 188: 1885. An account of the earlier literature of the subject will be found here.

[6] Th. W. Engelmann, Pflüger's *Arch.*, vol. xxxii. p. 80: 1883. The method employed by Engelmann to prove the occurrence of oxygen was peculiar. It was

certain infusoria, Vorticellæ, contain chlorophyl diffused in their plasma, which likewise gives off oxygen in sunshine.

It follows that a complete antithesis between interchange of force and matter in animals and plants does not exist;[1] and it will be henceforward impossible to separate the physiological chemistry of the vegetable from that of the animal world. The more our knowledge of each section of science advances, the more the two become fused together.

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based on the fact that certain bacteria, eager for oxygen, swarm round the cells containing chlorophyl. Compare the earlier and highly interesting treatises of Engelmann in Pflüger's *Arch.*, vol. xxv. p. 285: 1881; vol. xxvi. p. 537: 1881; vol. xxvii. p. 485: 1882; and vol. xxx. p. 95: 1883.

[1] Comp. Cl. Bernard, "Leçons sur les phénomènes de la vie, communs aux animaux et aux végétaux": Paris, 1878.

LECTURE IV

THE FOOD OF MAN—DEFINITION AND CLASSIFICATION OF FOOD-STUFFS—THE ORGANIC FOOD-STUFFS—PROTEID AND GELATIN

Our observations up to this point have shown us that the constituents of our body are subject to a constant circulation, to uninterrupted change. The materials, which we take into our body to replace the loss which is always going on in this circulation, are called food-stuffs. This is the definition of the term food-stuffs which is still met with in most text-books. But this definition is incomplete; it does not cover the whole meaning of food-stuffs; it dates from the time before the law of the conservation of energy was discovered. According to this definition, water would be the most important food-stuff, for our body contains 63 per cent. of water, which is constantly being given off by the lungs, the skin, and the kidneys; and this loss can only be replaced by the introduction of a fresh supply. The rudest form of empiricism, untutored common sense, is opposed to this interpretation, as no one would think of calling water 'nutritious.' Now, why is water not nutritious? For the simple reason that no potential energy is conveyed to the body by water. Water is a saturated compound; it as little produces movement as a stone lying on the ground. The stone cannot fall till it has been raised from the ground by the employment of kinetic energy; and not until the atoms of oxygen have been separated from the atoms of hydrogen and carbon by the kinetic energy of sunlight, is the plant enabled to store up that potential energy which gives rise to all the forms of kinetic energy contributing to animal life.

We shall therefore include under the term 'food-stuffs' those substances, which are a source of energy in the body, as well as those which replace the lost constituents of the body. There are substances in our food which never become integral constituents of our tissues, but which go to form a source of kinetic energy. To these belong the organic acids so widely diffused in vegetable food, such as tartaric acid, citric acid, and malic acid, which are never concerned in the formation of the tissues, but are burnt up to form carbonic acid and water, with the liberation of kinetic energy, which could be utilized for the performance of normal functions. To these we may perhaps add the carbohydrates, which likewise do not appear to be employed in the building up of tissues, although we know for a fact that they are the principal source of muscular work. Hence they are always circulating through all the organs of the body in the plasma of blood and lymph. They are indeed also found deposited in the tissues in the form of glycogen, but these deposits cannot be regarded as integral constituents of the living tissues; they are only stores of potential energy which disappear during muscular work; they are as little parts of our organism as coal is a part of the steam-engine.[1] The gelatin-yielding substances in our food, glutin, chondrin, osseïn, likewise serve only as sources of energy, and never assist in repairing the waste of tissue. The collagenous substances of our tissues are not formed from the collagenous but from the proteid constituents of food. But the gelatins in food are, as a matter of fact, split up and oxidized; they produce kinetic energy.

Inspired oxygen must also be reckoned among the food-stuffs. It is the only one which enters our tissues as a free element. It never becomes an integral constituent of our tissues, unless the loosely combined oxygen in the oxyhemoglobin of the blood-corpuscles may be considered so, but it is the most productive source of energy.

We have therefore to distinguish three classes of food-stuffs:—

1. Those which serve as sources of energy, and which can replace the exhausted constituents of the body. To this class belong proteids and fats.

2. Those which serve only as sources of energy. To this class belong carbohydrates, gelatins, oxygen.

3. Those which serve only to repair the waste of tissue, and

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[1] [This opinion must be received with some reserve, since it has been shown that the proximate constituents of all cells are the very complex bodies, tissue-fibrinogens, nucleo-albumins, &c., classed together under the term conjugated proteids. In nearly all cases, these substances yield a carbohydrate as one of the products of their decomposition, and we must therefore assume that carbohydrate forms a necessary integral constituent of the molecule. Even egg-albumin, one of the commonest of the so-called proteids, contains a carbohydrate moiety. In light of these results, it becomes doubtful whether any tissue, even muscle, can utilize carbohydrates directly for the production of energy, or whether these substances must not first be built up to form part of the living material of the cell.]

not as sources of energy. To this class belong water and the inorganic salts.

Our knowledge is at present too limited to permit of our giving a satisfactory and sharply defined classification of food-stuffs.

When a substance is split up and oxidized in our body, we do not know whether the kinetic energy thereby set free is really used up in the performance of normal functions, or whether it is given out as superfluous heat. In the latter case, the substance could not be regarded as a nutrient material, as it would be of no possible service to our organism. Alcohol may perhaps be cited as an example. In order to be of use in the performance of a normal function, a substance must split up and be consumed at the right time, at the right place, in a definite tissue. But we are not yet in a position to follow out the course of the substances taken up so closely as this.

It must moreover be borne in mind that certain substances, belonging to the second division, may indirectly assist in the building up of cells, by protecting the substances of the first class from decomposition and oxidation. Fats sometimes come under the first, and sometimes under the second heading; for, besides serving as stores of energy in the tissues, they are of great use in another way. The carbohydrates have, as we shall see, the power of changing into fats in the animal body, thus coming into the first instead of the second class. In short, the division is merely provisional.

We will now consider the separate group of food-stuffs in somewhat greater detail, beginning with proteids.

Proteids may be regarded as the most important food-stuffs, in so far as they are the only organic food-stuffs of which it can with certainty be affirmed that they are indispensable, and that they cannot be replaced by any other nutrient material. They are to be found in every animal and vegetable tissue; they form the chief part of every cell; they are never absent from any vegetable or animal food.

The various kinds of proteid which occur in the different animal and vegetable tissues present great differences in their chemical and physical properties. The question is therefore: What is included under the name proteid? Does it correspond to a clearly defined group of bodies? What have all varieties of proteid in common, and what distinguishes them from all other organic substances?

First, all proteids resemble one another in being composed of the same five elements, in proportions of weight not very remote from each other, and which vary within the following limits, according to the analyses hitherto made of the different proteids :—

Carbon	50.0 to 55.0	per cent.
Hydrogen	6.6 " 7.3	"
Nitrogen	15.0 " 19.0	"
Sulphur	0.3 " 2.4	"
Oxygen	19.0 " 24.0	"

Secondly, all proteids are alike in never occurring in true solution. Numerous clear liquids, containing proteids, are found in plants and animals, or may be artificially produced. But the fact that the proteid does not diffuse through animal membranes proves that it is not really dissolved in these liquids. The substances that are thus only apparently soluble have been termed "colloids" by Graham.[1]

If a solution of sodium silicate be poured into a vessel containing a large excess of dilute hydrochloric acid, the silicic acid thus set free remains apparently dissolved. By dialysis, the sodium chlorid thus formed and the excess hydrochloric acid may be got rid of, when a clear solution of pure silicic acid will remain in the dialyzer. The silicic acid may amount to 14 per cent. of the solution without its becoming thick and turbid ; it is readily poured out. But a few bubbles of carbonic acid passed through this solution suffice to coagulate the silicic acid, which is precipitated in the form of a jelly.[2] Grimaux[3] prepared a 2.26 per cent. solution of silicic acid, which was more stable, and which did not clot either in cold or upon warming when carbonic acid was passed through, but did so when heated, after the addition of common salt or of Glauber's salt.

The hydrate of alumina is soluble in a watery solution of aluminium sesquichlorid. If such a solution be placed in the dialyzer, the chlorid diffuses out, and the solution of pure alumina remains in the dialyzer as a clear, readily transferable fluid. This solution coagulates as soon as a small quantity of any salt is added. A 2 or 3 per cent. solution of alumina can be made to clot by the addition of a few drops of spring water ; it coagulates when poured from one glass into another, unless the glass has immediately before been washed out with distilled water.[4]

In a similar way as with the alumina, oxid of iron may be

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[1] Th. Graham, *Phil. Trans.*, vol. cli. part i. p. 183 : 1861.
[2] Graham, *loc. cit.*, p. 204.
[3] Grimaux, *Compt. rend.*, vol. xcviii. p. 1437 : 1884.
[4] Graham, *loc. cit.*, p. 207.

obtained as a clear blood-red apparent solution which is also very prone to coagulate.[1]

Grimaux found that an ammoniacal solution of oxid of copper also behaves like a colloidal substance, that it does not diffuse, and that it coagulates on dilution with water, on the addition of magnesium sulphate or of dilute acetic acid, or when exposed to a temperature of from 40° to 50° C.[2]

Many organic, as well as these inorganic colloidal substances, and all proteids, have the property of appearing in two forms, in apparent solution or in a coagulated form. The conditions, under which the proteids pass from one modification to the other, are very varying, and offer a method of classifying and distinguishing the many different kinds of proteid.[3] Some of them may, under appropriate conditions, be kept in solution by water alone; to these proteids belong serum-albumin and egg-albumin. Other kinds of proteid require the addition of alkaline chlorids in order to dissolve them; such are the globulins which are found in the blood, in muscle, in the white and yolk of egg, and probably in the protoplasm of every cell. If blood-serum be put in a dialyzer, the salts which hold the serum-globulins in solution diffuse out, and the globulins separate on the dialyzer as finely flocculent coagula, but the serum-albumin remains dissolved in the pure water.[4] There are other varieties of proteid which cannot be held in solution by alkaline chlorids, but only by basic alkaline salts, in which case neutralization of the alkalies with acids causes precipitation. The casein of milk and the artificial alkali-albumins belong to this category. Lastly, we come to the proteids which are so prone to coagulate, that they do so as soon as life is extinct in the tissues to which they belong. The coagulation of the blood and the phenomenon of muscular rigidity after death are connected with this fact. It even appears that these kinds of spontaneously coagulable albumin exist in every animal and vegetable cell. All proteids, without exception, pass from the soluble into the coagulated modification by

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[1] Graham, *loc. cit.*, p. 208.

[2] Grimaux, *loc. cit.*, p. 1435.

[3] A complete enumeration of all kinds of proteid and their distinguishing reactions would, I fear, weary the beginner, so I will refer him to the article "Eiweisskörper" (Proteids), in Ladenburg's "Handwörterbuch der Chemie." In this article E. Drechsel has given a very complete description and classification of the varieties of proteid, with a careful account of the literature of the subject (249 treatises).

[4] Aronstein, "Ueber die Darstellung salzfreier Albuminlösungen," Dissert.: Dorpat, 1873; and Pflüger's *Arch.*, vol. viii. p. 75: 1873. See also A. E. Bürckhardt, *Arch. f. exper. Path. u. Pharm.*, vol. xvi. p. 322: 1883; and G. Kauder *ibid.*, vol. xx. p. 411: 1886.

exposure to the boiling-point, provided they have a neutral or weakly acid reaction, and if neutral alkaline salts be present in considerable quantities. Silicic acid and many other colloids, as already stated, act in the same manner.

Concerning the inorganic colloidal substances, we know that besides occurring in these two modifications they also appear in nature in a third, viz., the crystalline form: silicic acid as rock-crystal, alumina as ruby, oxid of iron as specular iron ore.

This fact justifies us in hoping to obtain proteids likewise in a crystalline state. Not until we succeed in so doing, shall we be certain of having chemical individuals to deal with, and in a position to ascertain and compare their composition. The analysis and examination of pure proteid crystals and of all their products of decomposition would form the keynote of physiological chemistry.

Histologists have long been on the track of crystalline proteid. Under the microscope may be seen embedded in the seeds and glands of certain plants, little granules which have the appearance of incompletely formed crystals, and are therefore termed crystalloids, or aleuron-crystals. Similar structures may be seen in the yolk of egg of many animals, the so-called yolk-plates. By mechanical means, such as shaking the finely chopped materials with ether and other liquids, by washing, filtering, etc., these crystalloids may be isolated and obtained in considerable quantities. They give the proteid reactions and behave like globulins; they are soluble in a solution of common salt.[1] Maschke[2] has succeeded in recrystallizing the crystalloids of the para nut (*Bertholletia excelsa*). They dissolved in water at from 40° to 50° C., and the albumin separated out into crystals upon concentration of the solution. Schmiedeberg[3] obtained crystalline compounds of the same proteid with alkaline earths, the crystalloids being mostly soluble in distilled water at from 30° to 35° C. When a stream of carbonic acid is passed through the clear filtered solution, globulin is precipitated. If this precipitate is treated with magnesia and water, the magnesia compound of the globulin is dissolved. From this solution, when concentrated at from 30° to 35° C., the magnesia compound of the globulin is separated out as well-formed peculiarly glistening polyhedral crystals, of the size of poppy-seeds. If a little calcium chlorid or barium chlorid be

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[1] Th. Weyl, *Zeitschr. f. physiol. Chem.*, vol. i. p. 84: 1877; containing also an account of the earlier literature of the subject.

[2] O. Maschke, *Botan. Zeitg.*, p. 411: 1859.

[3] O. Schmiedeberg, *Zeitschr. f. physiol. Chem.*, vol. i. p. 205: 1877.

added to the solution before concentration, we obtain the calcium and barium salts of the globulin in fine crystals.

The fact that these crystals are not free proteid, but compounds of proteid with substances of known atomic weight, presents a great advantage, in that it enables us to make an exact analysis of this compound, and thus determine the molecular weight of the proteid.

Drechsel[1] found 1.40 per cent. MgO in the crystals of the magnesia compound, which he obtained according to Schmiedeberg's method, drying them at 110° C. From this, the molecular weight of the proteid has been reckoned—

$$\frac{x}{40} = \frac{100 - 1.40}{1.4}; \; x = 2817.$$

By the following alteration in Schmiedeberg's method, Drechsel succeeded in more perfectly crystallizing the magnesia compound. Instead of concentrating the solution, he introduced it into a dialyzer, which he placed in absolute alcohol. In proportion as the alcohol took the place of the water, crystalline granules continued separating out of the solution. The determination of the magnesia in the crystals dried at 110° C. gave 1.43 per cent. MgO, or nearly the same as in the first preparation. The molecular weight of the proteid thus calculated is 2757. On the other hand, the amount of water varied in each preparation, the first yielding 7.7 per cent., the second 13.8 per cent. of water, both at 110° C.

By a similar method, with the alcohol dialyzer, Drechsel succeeded in producing a sodium compound of the same globulin. At 110° C. this yielded 15.5 per cent. of water, and contained in a dry state 3.98 per cent. Na_2O. From this the proteid molecule is found to be equal to 1496, or nearly half as great as in the calculation from the magnesia compound. If the smaller molecular weight be accepted, we must conceive that a bi-valent atom of magnesium links two molecules of proteid. If we accept the double weight, the molecule must contain two hydrogen atoms, which are replaced by sodium atoms. The amount of incinerated proteid was moreover much too small to allow of an exact estimate of the molecular weight. The absolute amount of the MgO weighed 0.0050 and 0.0065 grm.; that of the Na_2CO_3 weighed 0.0773 grm. It would be of great interest to determine with accuracy the relation of sulphur to sodium by a series of careful analyses, in which large quantities of proteid were incinerated. Supposing that no whole number of sulphur atoms went to one atom of sodium,

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[1] E. Drechsel, *Journ. f. prakt. Chem.* N.F., vol. xix. p. 331: 1879.

but a whole number and a fraction, then the denominator of the fraction would have to be multiplied by the equivalent of the albumin molecule, calculated from the proportion of sodium. No one has hitherto been found to undertake such a troublesome experiment, and we therefore know nothing concerning the size of proteid-molecules.

The most thorough investigations upon proteid-crystals have been carried out by G. Grübler,[1] under Drechsel's guidance. They succeeded in recrystallizing the crystalloids of pumpkin-seeds by preparing at 40° C. saturated solutions of globulin in salt solutions, such as sodium chlorid, ammonium chlorid, magnesium sulphate, from which the albumin separated out in crystals on very slow cooling. These crystals were regular octahedra, and when incinerated left only 0.11 to 0.18 per cent. of ash, which consisted of alkalies, lime, magnesia, iron, and phosphoric acid. When incinerated with potash, 0.23 per cent. P_2O_5 was obtained.

The elementary analysis of Grübler's proteid-crystals gave the following mean, obtained from a series of analyses which agreed well with each other :—

	Proteid-crystals from sodium chlorid solution.	Proteid-crystals from ammonium chlorid solution.	Proteid-crystals from magnesium sulphate solution.
Carbon	53.21	53.55	53.29
Hydrogen	7.22	7.31	6.99
Nitrogen	19.22	19.17	18.99
Sulphur	1.07	1.16	1.13
Oxygen	19.10	18.70	19.47
Ash	0.18	0.11	0.13

Grübler has also produced a crystalline combination of the same proteid with magnesia: the crystals separating out on slow cooling of a solution (obtained at 40° C.) of the proteid and magnesia in water. The crystals showed the following composition :—

	Dry matter.	Matter free from ash.
Carbon	52.66	52.98
Hydrogen	7.20	7.25
Nitrogen	18.92	18.99
Sulphur	0.96	0.97
Oxygen	19.74	19.81
Ash	0.52	
MgO	0.45	

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[1] G. Grübler, "Ueber ein krystallinisches Eiweiss der Kürbissamen," *Journ. f. prakt. Chem.*, vol. xxiii. p. 97 : 1881.

The following formula for the magnesium compound of globulin may be made out from the percentage composition :—

$$C_{1170}H_{1920}N_{360}O_{332}S_8Mg_3.$$

It is to be regretted in this analysis that the quantity of incinerated proteid was again far too small for an exact estimate of the magnesium and sulphur. The absolute weight of the barium sulphate was 0.0521 grm., that of the pyrophosphate of magnesia 0.0166 grm.

If we assume the presence of only one atom of magnesium in the magnesium compound, as Grübler did in his computation, then the size of the molecule would be 8848. But our calculation shows that for each atom of magnesium we must claim $2\frac{2}{3}$ atoms of sulphur.

$$\frac{x.32}{40}=\frac{0.96}{0.45};\quad x=\frac{8}{3}.$$

The molecule of the magnesium compound must therefore be taken as three times larger. It is conceivable that the three bivalent magnesium atoms may link four proteid molecules, and that only two atoms of sulphur are contained in each. Every proteid molecule would then have the following composition :—

$$C_{292}H_{481}N_{90}O_{83}S_2.$$

From this point of view, we attain to the smallest molecular weight of which analysis admits. But this supposition is quite arbitrary, and the molecular weight probably a multiple of that calculated.

Ritthausen,[1] adopting the methods of Drechsel and Grübler, produced crystalline proteid from hemp and castor-oil seeds. The elementary analysis gave the following percentage composition :—

	Globulin from hemp seed.	Globulin from castor-oil seed.
Carbon	50.92	50.85
Hydrogen	6.91	6.97
Nitrogen	18.71	18.55
Sulphur	0.82	0.77
Ash	0.11	0.057
Oxygen	22.53	22.80

Hemoglobin,[2] the red coloring matter of the blood, also belongs to the proteid compounds capable of crystallization.

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[1] Ritthausen, *Journ. f. prakt. Chem.*, N. F., vol. xxv. p. 130 : 1882.

[2] The discoverer of the hemoglobin crystals was A. Boettcher, and the first analyses of them were carried out by my revered teacher, Carl Schmidt, in Dorpat. See A. Boettcher, "Ueb. Blutkrystalle" : Dorpat, 1862.

This substance forms the chief constituent of the red blood-corpuscles, and is the compound of a proteid with a body of known composition containing iron, called hematin. An exact analysis of completely pure hemoglobin crystals has been carried out by Zinoffsky,[1] who went on recrystallizing the hemoglobin crystals obtained from horse's blood, until the dry residue of the solution showed the same amount of iron as the dry crystals. The elementary analysis of these crystals yielded the following results:—

Carbon	51.15
Hydrogen	6.76
Nitrogen	17.96
Sulphur	0.389
Iron	0.336
Oxygen	24.425

The relation of the sulphur atom to the iron atom may, from Zinoffsky's analysis, be calculated thus—

$$\frac{x.32}{56} = \frac{0.3890}{0.3358}; \quad x = 2.03.$$

Exactly two atoms of sulphur combine with one atom of iron, and the formula of the hemoglobin is found to be—

$$C_{712}H_{1130}N_{214}O_{245}FeS_2.$$

If the molecule of the hematin, $C_{32}H_{32}N_4O_4Fe$, be subtracted, the formula of the proteid is obtained—

$$C_{680}H_{1098}N_{210}S_2O_{241}.$$

A. Jaquet[2] found that exactly three atoms of sulphur go to one atom of iron in the hemoglobin of dog's blood. The analysis gave the formula:—

$$C_{758}H_{1203}N_{195}S_3FeO_{218}.$$

After subtraction of the hematin it is:—

$$C_{726}H_{1171}N_{194}S_3O_{214}.$$

The calculation is not quite exact, because the splitting up of the hemoglobin into proteid and hematin occurs only by

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[1] O. Zinoffsky (Bunge's laboratory), "Ueber die Grösse des Hämoglobinmoleküls," Dissert.: Dorpat, 1885; reprinted in the *Zeitschr. f. physiol. Chem.*, vol. x. p. 16: 1885.

[2] Alfred Jaquet (Bunge's laboratory), "Beitr. z. Kenntniss des Blutfarbstoffes," Dissert.: Basel, 1889; or the *Zeitschr. f. physiol. Chem.*, vol. xii. p. 285: 1888.

the absorption of water and oxygen.[1] A few hydrogen and oxygen atoms must therefore be added to the above proteid formulæ. Nevertheless they are perhaps the most exact that have been computed from the proteid analyses hitherto made, and may serve for present guidance.

Harnack[2] has produced and analyzed a proteid compound which, though amorphous, is probably pure. Harnack precipitated neutral solutions of egg-albumin with solutions of copper, and obtained the noteworthy result that, although the quantitative relation of the albumin and of the copper salt varied greatly, yet in the precipitates the albumin combined with the oxid of copper was only found in two perfectly definite proportions. The precipitates contained either from 1.34 to 1.37, a mean of 1.35 per cent. Cu, or from 2.56 to 2.68, a mean of 2.64 per cent. Cu; in one case therefore exactly twice as many copper atoms as in the other.

The complete elementary analysis gave a mean from a series of estimates agreeing well with each other:—

	I.	II.
Carbon	52.50	51.43
Hydrogen	7.00	6.84
Nitrogen	15.32	15.34
Sulphur	1.23	1.25
Copper	1.35	2.64

According to the first analysis, the relation of the sulphur atom to the copper atom may be calculated as—

$$\frac{x.32}{63.4} = \frac{1.23}{1.36}; \quad x = 1.805.$$

The second analysis makes $x = 0.938$. In these analyses also, the incinerated residue was much too small to allow a determination of the copper and sulphur.[3] A more exact determination of these elements is urgently required. From his analyses, Harnack reckons the formula for the first compound:

$$C_{204}H_{320}N_{52}O_{66}S_2Cu.$$

Loew[4] has produced two silver compounds of egg-albumin, which correspond to Harnack's copper compounds; one con-

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[1] Concerning this, see Max Lebensbaum, *Wien. Sitzungsber.*, vol. xcv. part ii., March, 1887. In this work, carried out in Berne under Nencki's direction, there is also an account of the earlier literature on the splitting up of hemoglobin. Compare also Hoppe-Seyler, *Zeitschr. f. physiol. Chem.*, vol. xiii. p. 477: 1889.

[2] E. Harnack, *Zeitschr. f. physiol. Chem.*, vol. v. p. 198: 1881.

[3] Compare O. Loew, Pflüger's *Arch.*, vol. xxxi. p. 393: 1883.

[4] O. Loew, *loc. cit.*, p. 402.

tained from 2.2 to 2.4 per cent. Ag, the other a mean of 4.3 per cent. Ag. Taking Harnack's figures for the amount of copper, the silver equivalent may be computed = 2.3 per cent. and 4.5 per cent. These facts go to prove that Harnack's and Loew's preparations were true chemical entities. It is to be regretted that Loew has not made any elementary analysis of his preparations.

Finally Franz Hofmeister[1] has succeeded in crystallizing egg-albumin itself. The white of the hen's egg contains two kinds of proteid substances, one belonging to the albumin and the other to the globulin group. If the globulins are precipitated by a concentrated solution of ammonium sulphate, and the filtrate from this precipitate be allowed to stand for some days exposed to slow evaporation, small spheroids separate out, which are composed of incompletely formed crystals. By dissolving and recrystallizing these spheroids, albumin is obtained in well-formed, needle-shaped crystals. Analysis of these crystals gave the following composition :—

C	53.3
H	7.3
N	15.0
S	1.1
O	23.3

Using Hofmeister's method, Bondzynski and Zoja[2] prepared albumin crystals from white of egg, and succeeded, by fractional crystallization, in demonstrating the existence in white of egg of several distinct albumins, differing by their solubilities in ammonium sulphate solutions as well as by their coagulation temperatures and their rotatory power on polarized light. On the other hand, the elementary composition was identical in all the fractions. In one preparation the lime and phosphoric acid were also determined, and the following composition was arrived at :—

C	52.3
H	.71
N	15.5
S	1.6
O	23.5
P_2O_5	0.29
CaO	0.26

The ash forms part of the constitution of the proteid molecule. Proteid free from ash never occurs in nature. Although it

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[1] Franz Hofmeister, *Zeitschr. f. physiol. Chem.*, vol. xiv. p. 165 : 1889, and vol. xvi. p. 187 : 1892. Compare also S. Gabriel, *idem*, vol. xv. p. 456 : 1891.

[2] St. Bondynski and L. Zoja, *Zeitschr. f. physiol. Chem.*, vol. xix. p. 1 : 1894.

can be prepared artificially,[1] we have not yet succeeded in crystallizing it.

Bondzynski and Zoja could not obtain the globulins of white of egg in a crystalline form; the only precipitates they obtained were in the form of the spheroids, which are the first stage in the crystallization of albumin.

In blood-serum, as in the white of egg, we also find albumins and globulins (compare Lect. XIV.). In albuminuria both escape into the urine, but in very varying proportions. Until quite recently no spontaneous crystallization of the proteids in the urine had ever been observed. It seems however that the presence of one kind of proteid hinders the crystallization of the other, since in a recent case of marked albuminuria, published by Byrom Bramwell and Noel Paton,[2] where almost only globulin was present, this globulin could be easily crystallized by Hofmeister's method. Indeed at times it was sufficient to allow the urine to stand for one or two days to obtain a crystalline silky precipitate, which under the microscope was seen to consist of beautiful rhombic prisms. The analysis of these globulin crystals gave the following results :—

C	51.9
H	6.9
N	16.1
S	1.2
O	33.9

Finally, we may mention that Gürber[3] and Michel[4] have succeeded in preparing beautiful crystals of the albumin of blood-serum. [The technique of the crystallization of proteids has been much simplified by the discovery of Hopkins that the addition of a trace of acid much favors the ease of crystallization. Full details of the method will be found in the original paper.[5] By this method it is possible to prepare crystals, in any quantity and within a few hours, both of egg- and serum-albumin. By washing these crystals with an acid solution of sodium chlorid, the whole of the ammonium sulphate may be removed, showing that the presence of this salt is not necessary to the integrity of the crystalline form.]

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[1] See letter written by Liebig to Wöhler, Nov. 16, 1848 (Aus J. Liebig's u. Fr. Wöhler's Briefwechsel, vol. i. p. 323; Braunschweig, Vieweg u. Sohn, 1888); E. Harnack, *Ber. d. deut. chem. Ges.*, vol. xxiii. p. 40: 1890, and vol. xxv. p. 204: 1892; K. Bülow, Pflüger's *Arch.*, vol. lviii. p. 207: 1894.

[2] Byrom Bramwell and D. Noel Paton, *Reports fr. the Lab. of Roy. Coll. of Physicians, Edin.*, vol. iv. p. 47: 1892.

[3] A. Gürber, *Sitzungsber. d. phys.-med. Ges. zu Würzburg*, p. 143: 1894.

[4] A. Michel, *Verh. d. phys.-med. Ges. zu Würzburg*, vol. xxix. No. 3: 1895.

[5] F. Gowland Hopkins and S. N. Pinkus, "Crystallization of Proteids," *Journ. of Physiol.*, vol. xxiii. p. 130: 1898.

The formulæ of the proteids already quoted are:—

Egg-albumin, $C_{204}H_{322}N_{52}O_{66}S_2$.
Proteid in hemoglobin of horse, $C_{680}H_{1098}M_{210}O_{241}S_2$.
Proteid in hemoglobin of dog, $C_{726}H_{1171}N_{194}O_{214}S_3$.
Globulin from pumpkin-seeds, $C_{292}H_{481}N_{90}O_{83}S_2$.

Thus if we select the most careful and exact of all the analyses hitherto made of the purest preparations of different proteids, we find that they give very varying quantitative compositions, and that they particularly differ in the amount of sulphur.

So far as they have been investigated, proteids show a certain agreement in their products of decomposition. It appears that the different proteids are composed of the same proximate constituents combined in varying proportions. On heating the proteids with baryta water, they break up under hydration into numerous compounds, which are almost all of known constitution. The principal are carbonic acid, oxalic acid, acetic acid, ammonia, sulphuretted hydrogen, sulphuric acid, and a number of amido-acids, such as aspartic acid, leucin, tyrosin, as well as lysin, lysatin, &c. The same amido-acids, as well as ammonia and the bases lysin, lysatin, azginin, and histidin,[1] also present themselves on boiling the proteids with acids and under the influence of ferments. We shall have to discuss the products produced by the splitting up of proteids more fully when we come to treat of the chemistry of the urine; we shall then also consider the decomposition of the nitrogen compounds in the organism (*vide* Lecture XIX.).

Another group of food-stuffs, the GELATINIFEROUS OR COLLAGENOUS SUBSTANCES, are closely related to the proteids in chemical qualities; but their physiological import is quite different.

Gelatiniferous substances are the chief constituents of connective tissue, of bone and cartilage, and therefore form an important part of the food of carnivorous and omnivorous animals.

Gelatins, like proteids, are colloids containing nitrogen and sulphur, and may likewise occur in two modifications—one apparently dissolved but not diffusible; the other coagulated. But the conditions of the transit from one modification to another are exactly the reverse. All proteids coagulate, as

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[1] Kossel, *Sitzungsber. d. Ges. z. Beförd. d. ges. Naturwissensch.*, Marburg, p. 56: July, 1897. Here also references will be found to the earlier authors who have dealt with these bases.

already described, at boiling-point, with neutral or weakly acid reaction, and in the presence of salts; the gelatins, on the contrary, become soluble under these circumstances,[1] and on cooling the solution of gelatin thus formed again coagulates. Solutions of proteid are precipitated by mineral acids, but not so solutions of gelatin. The gelatin of cartilage is certainly precipitated by very dilute mineral acids, but dissolved by an excess, thus behaving in the opposite manner to the globulins, which are soluble in very dilute (1 per 1000) hydrochloric acid, but are again precipitated by an excess of it.

If therefore varieties of proteid or gelatin are soluble or coagulable under opposite conditions, we need not be surprised to find that, under similar conditions in the organism, the one occurs invariably in the soluble, the other only in the solid, modification. Proteids are found in our bodies only in a liquid state. In this form they are the main constituents of the blood-plasma and of lymph, or they occur in that peculiar semi-liquid modification common to all those tissues which play an active part in the functions of our bodies: the contractile contents of muscle-fibers, the axis-cylinders of nerve-fibers, the protoplasm of all cells which we must not conceive as rigid structures, but as engaged in a constant state of active ameboid movement.[2] The collagenous substances, on the contrary, are found in our tissues only in the rigid modification; they form the supports and the framework of our bodies, viz., bone, cartilage, ligaments, and connective tissue of all kinds.

But here I must guard against a misunderstanding, lest it should appear that I am identifying the gelatiniferous constituents of the tissues with coagulated gelatin. In the conversion of collagenous tissues into solutions of gelatin, a fundamental change takes place, possibly a decomposition accompanied by hydration, and the gelatin is not reconverted into the collagenous substances on coagulation.

The percentage composition of the varieties of gelatin is nearly the same as that of the proteids. At the same time, it is characteristic of the former that they are somewhat poorer in

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[1] It is not until after the phosphates and carbonates of lime and magnesia have been extracted with dilute hydrochloric acid at a low temperature, that the gelatin of bone is dissolved in boiling water, and especially under increased pressure. The salts of lime and magnesia appear to be chemically united with the collagenous substance.

[2] As already mentioned, proteid is found in the solid form, deposited in crystals, only in the yolk of egg and in the seeds and bulbs of plants. These crystalloids are however not integral constituents of the living tissue, but dead material, the store of nutriment for the future development of the germ.

carbon and richer in oxygen; they are products of the initiation of the breaking up and oxidation of the proteids in the animal body. According to the analyses[1] hitherto made, the percentage composition of the gelatins varies within the following limits:—

	Gelatin from bone or connective tissue.	Chondrin.	Albumin.
Carbon	49.3—50.8	47.7—50.2	50.0—55.0
Hydrogen.	6.5— 6.6	6.6— 6.8	6.6— 7.3
Nitrogen	17.5—18.4	13.9—14.1	15.0—19.0
Sulphur.	— 0.56(?)	0.4— 0.6(?)	0.3— 2.4
Oxygen	24.9—26.0	29.0—31.0	19.0—24.0

We know for a fact that certain compounds of the aromatic class, rich in carbon and which issue in the form of tyrosin and indol from the decomposition of proteids, are absent in the gelatiniferous substances.[2] It is moreover a fact that the heat-equivalent of gelatin is lower than that of the proteids;[3] that therefore a part of the potential energy introduced into the animal body by proteid is already consumed during its conversion into gelatin-yielding substances. We should therefore, *à priori*, expect to find that the gelatins do not replace the proteids of the food, and that they cannot form the proteids of

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[1] Fr. Hofmeister, *Zeitschr. f. physiol. Chem.*, vol. ii. p. 299: 1878.

[2] The absence of tyrosin explains the fact that gelatin does not give Millon's reaction, which is common to all proteids (red coloration on boiling with nitrate of mercury, with the addition of fuming nitric acid). All aromatic oxy-acids and their derivatives, to which tyrosin belongs, give this reaction. On the other hand, compounds which are wanting in proteids occur among the decomposition-products of gelatins. Amido-acetic acid (glycin, glycocoll), which has hitherto not been shown to exist among the decomposition-products of any proteid, is obtained from the gelatin of bones and connective tissue, on boiling with alkalies and acids, and in putrefaction. From cartilage Schmiedeberg (*Arch. f. exp. Path. u. Pharm.*, vol. xxviii. p. 355 : 1891) isolated small quantities of a compound, which on boiling with dilute acids was dissociated with the formation of sulphuric acid, acetic acid, glycuronic acid, and glycosamin. These results explain the older statements as to the occurrence of sugar or 'reducing substances' among the decomposition-products of chondrin. On the products of the decomposition of proteids and gelatin, see further, M. Nencki, "Ueber die Zersetzung der Gelatine und des Eiweisses bei der Fäulniss mit Pankreas," Bern., 1876; and *Sitzungsber. d. Akad. d. Wissensch. in Wien, Math.-natur. Klasse*, vol. xcviii. Pt. 2, May 9, 1889; Jules Jeanneret, *Journ. f. prakt. Chem.*, N. F., vol. xv. p. 353: 1877; Leon Selitrenny, *Sitzungsber. d. Akad. d. Wissensch. in Wien, Math.-natur. Klasse*, vol. xcviii. Pt. 2, b. Dec. 12, 1889 (from Nencki's laboratory); Ed. Buchner und Th. Curtius, *Ber. de deutsch. chem. Ges.*, vol. xix. p. 850: 1886; and R. Maly, *Sitzungsber. d. Kais. Akad. d. Wissensch. in Wien, Math.-natur. Klasse*, vol. xcviii. Jan. 6, 1889.

[3] Danilewsky, *Centralblatt f. d. med. Wissensch.*, Nos. 26 and 27: 1881.

the tissues. Such a conversion would be opposed to the whole tendency of animal metabolism, which is essentially a process of decomposition and of oxidation. The conversion of gelatin into albumin would be one of synthesis and reduction. The results of Voit's experiments,[1] showing that gelatin cannot replace proteid in the food, are in agreement with the *à priori* deduction. When Voit fed dogs exclusively on gelatin, or on gelatin and fat, they excreted more nitrogen than they took in with their food; they therefore used up the proteids of their tissues. But if to a small amount of the proteid in the food, which was not by itself sufficient to prevent a loss of tissue-proteid, gelatin was added, the nitrogenous equilibrium was restored. The gelatin therefore had preserved the proteid of the tissues from decomposition; it acts as a 'proteid sparer.' This proteid-sparing action is also shared by fats and carbohydrates; but, as Voit's experiments have shown, not in the same degree as by gelatin.

It has recently been supposed that the gelatin might perhaps replace the proteid if tyrosin were at the same time administered. We now know that the contrast in the metabolism of animals and plants is not so complete as was formerly supposed. Hence there was the *à priori* possibility that proteid might be formed by synthesis from gelatin and tyrosin. The first experiments[2] appeared even to favor this supposition; but on careful repetition, a negative result was obtained. Lehmann[3] fed two rats on a mixed diet of gelatin, rice-starch, butter, meat-extract, and bone-ash; and six rats on the same diet with the addition of tyrosin. They all died at about the same time, from forty-seven to seventy days afterwards. Thus these experiments also tend to show that no proteid can be

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[1] Voit, *Zeitschr. f. Biolog.*, vol. viii. p. 297: 1872. The historical introduction to this treatise, showing the numerous errors into which any one would necessarily fall from the experiments, formerly made to decide the question concerning the nutritive value of gelatin, is highly instructive and interesting. Compare also the more recent paper on this subject: *Zeitschr. f. Biolog.*, vol. x. p. 203: 1874. We cannot attain to a complete understanding of the significance of food-stuffs until we get to know all the processes of metabolism. We ought therefore properly to leave the consideration of the import of the various food-stuffs to the last chapter of physiological chemistry. But this difficulty can in no way be surmounted, for every chapter of physiology presupposes other chapters. It appears to me advisable to arouse the reader's interest at the start by pointing out the importance in vital processes of those substances whose gradual changes and ultimate destination in the animal body must be the foundation of all future study.

[2] L. Hermann und Th. Escher, *Vierteljahrschr. der naturforsch. Ges. in Zürich*, p. 36: 1876.

[3] Karl B. Lehmann, *Sitzungsber. d. Ges. f. Morphol. u. Physiol. in München*: 1885.

produced from gelatin, although we know, on the other hand, that all gelatin-yielding tissues of the body are formed from proteid. This is seen in the growth of the herbivora, and of the young animal in its suckling stage, since their food contains proteids but no gelatin.

Gelatin, as such, is to be found only in cooked food. Of the gelatin-yielding tissues, connective tissue is easily digested, and is therefore an important element of food. Meat, which consists to a great extent of connective tissue, disappears almost entirely in the alimentary canal of man. The digestibility of cartilage and bone was long doubted, until it was proved, by experiments in Voit's laboratory,[1] that dogs fed on cartilage ejected but a very inconsiderable amount in the feces. A large part (as much as 53 per cent.) of the collagenous substance of the bones did not reappear in the feces. We do not know how far the digestive organs of man are capable of dealing with cartilage and bone, as no experiments have been made to ascertain this.

Keratin, the chief constituent of the epidermis, of hair, nails, claws, hoofs, horns, and feathers, was formerly classed with the collagenous substances. But keratin is distinguishable from the gelatins, as well as from the proteids, by its high percentage of sulphur (from 4 to 5 per cent.) but more especially from the gelatins by the fact that tyrosin makes its appearance among its products of decomposition. According to this last property keratin should be classed among the proteids. The keratins of the various tissues are probably not identical and not chemical entities, but mixtures of different substances. Keratin does not come under our consideration as a food; according to previous experiments it appears incapable of being digested by the mammal.[2] Certain insects can digest keratin. The caterpillar of the clothes-moth apparently feeds almost entirely upon keratin. Wherever therefore keratin is rendered soluble, it can take the place of proteid. The chief constituent of elastic tissue, 'elastin,' which was likewise formerly classified under the same heading as gelatin, now stands by itself: on decomposition, it yields a small amount of tyrosin.[3] Elastic tissue is almost completely

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[1] J. Etzinger, *Zeitschr. f. Biolog.*, vol. x. p. 84: 1874.

[2] Knieriem, "On the Value of Cellulose in the Animal Organism," p. 6, Jubilee Essay: Riga, 1884. Reprinted in the *Zeitschr. f. Biolog.*, vol. xxi. p. 67: 1885.

[3] For the composition and properties of elastin, *vide* R. H. Chittenden und A. S. Hart, *Zeitschr. f. Biolog.*, vol. xxv. 368: 1889. The earlier literature is here quoted.

digested by dogs.[1] As regards human beings, we must mention an experiment made by Horbaczewski[2] on a patient with gastric fistula. Powdered elastin in a small bag was introduced through the fistula, and was found to be partly dissolved in twenty-four hours.

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[1] Etzinger, *loc. cit.* Compare also L. Morochowetz, *St. Petersburger med. Wochenschr.:* No. xv., 1886; A. Ewald und W. Kühne, *Verhandlungen des natur.-histor. med. Vereins zu Heidelberg,* N. F., vol. i. p. 441: 1877; and Chittenden und Hart, *loc. cit.*

[2] J. Horbaczewski, *Zeitschr. f. physiol. Chem.*, vol. vi. p. 330: 1882.

LECTURE V

THE ORGANIC FOOD-STUFFS (*continued*) — CARBOHYDRATES AND FATS—SIGNIFICANCE OF THE THREE MAIN GROUPS OF ORGANIC FOOD-STUFFS

WE will now turn our attention to two main groups of food-stuffs which offer a contrast to the two last mentioned, in being free from nitrogen and sulphur—the FATS and the CARBOHYDRATES.[1] They agree with one another in being made up of the same three elements: carbon, hydrogen, and oxygen. But the quantitative composition is well known to be quite different; the fats are much poorer in oxygen, and richer in carbon and hydrogen. Therefore the heat-equivalent of the fats is much greater.

The heat-equivalent of the organic substances can not be exactly computed from the known heat-equivalents of carbon and hydrogen, because, of the amount of heat which is set free by the union of the oxygen with the carbon and hydrogen, a part which is used up in the separation of the hydrogen atoms from the carbon atoms, and of the carbon atoms from each other. This amount of heat may vary greatly in different compounds, because the atoms are more or less firmly combined with each other, and varying amounts of heat are set free by their union. Metameric compounds are known to produce different heat-equivalents. Hence the heat-equivalents of food stuffs have been determined by direct calorimetric methods, first by Frankland,[2] then by an improved method by Stohmann [3] and his pupil Rechenberg,[4] lastly by Danilewsky [5] and by Rubner.[6] In the following table I give the values ascertained

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[1] Both here and in all subsequent remarks, a knowledge of the chemical properties of the carbohydrates and fats is presupposed, as these compounds are usually described at sufficient length in the text-books of organic chemistry.

[2] Frankland, *Philos. Mag.*, vol. xxxii. p. 182: 1866.

[3] Stohmann, *Journ. f. prakt. Chem.*, N. F., vol. xix. pp. 115–142: 1879; and *Landwirthschaftl. Jahrb.*, pp. 531–581: 1884; *Zeitschr. f. Biolog.*, vol. xxxi. p. 364: 1895.

[4] von Rechenberg, *Journ. f. prakt. Chem.*, N. F., vol. xxii. pp. 1–45, 223–250: 1880.

[5] Danilewsky, Pflüger's *Arch.*, vol. xxxvi. p. 237: 1885.

[6] Rubner, *Zeitschr. f. Biolog.*, vol. xxi. pp. 250, 337: 1885.

by the above-mentioned authors. By the side of each figure will be found the first letters of the author's name. The heat-equivalents of carbon, hydrogen, and of a few decomposition-products of food-stuffs, are also added to the table for reference in future remarks. The unit of heat (calorie) is that quantity of heat required to raise the temperature of one gramme of water 1° C.

HEAT-EQUIVALENTS OF ONE GRAMME OF SUBSTANCE EXPRESSED IN CALORIES.

Hydrogen	F. and S.[1]	34,462
Stearic acid, $C_{18}H_{36}O_2$	Rch.	9886
“	Rub.	9745
“	F. and S.	9717
Beef fat	D.	9686
Olive oil	St.	9455
Pig's fat	Rub.	9423
Stearic acid	St.	9412
Fat (human and animal), the average of a number of approximate figures, 9319–9429	St.	9372
Butter	St.	9179
Charcoal	F. and S.	8080
Ethylalcohol	F. and S.	7184
“	Berthelot	6980
Leucin	St. and L.[2]	6525
“	B. and A.[3]	6537
Fibrin (vegetable)	D.	6231
Elastin	St. and L.	5961
Hemoglobin (from horse)	D.	5949
Vegetable fibrin	St. and L.	5942
Serum-albumin	St. and L.	5918
Tyrosin	B. and A.	5916
Hemoglobin (from horse)	B. and A.	5915
Syntonin	St. and L.	5908
Hemoglobin	St. and L.	5885
Casein	St. and L.	5858
“	D.	5855
Legumin	St. and L.	5793
Blood fibrin	D.	5772
Vitellin	St. and L.	5745
Egg-albumin	St. and L.	5735
Milk-casein (three preparations 5754–5693), average	St.	5715
Egg-albumin	B. and A.	5690
Crystallized albumin (from pumpkin-seeds)	St. and L.	5672
Hippuric acid	St. and L.	5668
“ “	B. and A.	5659
Butyric acid	F. and S.	5647

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[1] Favre and Silbermann, *Ann. d. Chim. et d. Phys.*, vol. xxxiv. p. 357: 1852.

[2] F. Strohmann and H. Langbein, *Journ. f. prakt. Chem.*, N. F., vol. xliv. p. 336: 1891.

[3] Berthelot and A. André, *Ann. d. Chim. et d. Phys.*, series vi. vol. xxii. pp. 5 and 25: 1891.

HEAT-EQUIVALENTS OF ONE GRAMME OF SUBSTANCE EXPRESSED IN CALORIES (*continued*).

Paraglobulin (from horse's serum)		5634
Casein	B. and A.	5629
Crystallized proteid (prepared by Grübler from pumpkin seeds)	St.	5595
Egg-albumin (two preparations, 5556 and 5597), mean	St.	5577
Blood fibrin (three preparations, 5487-5536), average	St.	5508
Gelatin (from isinglass)	D.	5493
Ossein	B. and A.	5414
Chrondrin	B. and A.	5346
Peptone	St. and L.	5299
Caffein	St. and L.	5231
Chondrin	St. and L.	5131
Ossein	St. and L.	5040
Peptone (prepared by Drechsel)	D.	4914
Chondrin	D.	4909
Peptone	D.	4876
Sarcosin	St. and L.	4506
Starch	Rch.	4479
Erythrodextrin	Rch.	4325
Glycerin	St.	4305
Creatin (anhydrous)	St. and L.	4275
Cane sugar	D.	4176
“ “	Rch.	4173
Maltose anhydride	Rch.	4163
Lactose anhydride	Rch.	4162
Cellulose (from Swedish filter-paper)	St.	4146
Starch	St.	4116
Cane sugar	St.	3959
Lactose hydrate, $C_{12}H_{22}O_{11}$, H_2O	Rch.	3945
Dextrose anhydride	Rch.	3939
Maltose hydrate, $C_{12}H_{22}O_{11}$, H_2O	Rch.	3932
Guanin	St. and L.	3892
Lactose anhydride	St.	3877
Creatin $+ H_2O$	St. and L.	3714
Dextrose anhydride	St.	3692
Lactose hydrate	St.	3667
Dextrose hydrate, $C_6H_{12}O_6$, H_2O	Rch.	3567
Acetic acid	F. and S.	3505
Aspartic acid	St.	3423
Glycocoll	St.	3050
Succinic acid	Rch.	2996
“ “	St.	2937
Aspartic acid	B. and A.	2911
“ “	St. and L.	2899
Uric acid	St. and L.	2750
“ “	Frankl.	2645
“ “	St.	2620
Urea	St. and L.	2542
“	D.	2537
“	St.	2465
“	Frankl.	2121
Tartaric acid	St.	1744
“ “	Rch.	1407
Oxalic acid	Rch.	659
“ “	St.	569

In the case of non-nitrogenous food-stuffs, the same amounts of heat are produced in our bodies as in the calorimeter, because the ultimate products are the same; but it is different in the case of food-stuffs containing nitrogen. Nitrogen is liberated in a free state from combustion in the calorimeter; on the other hand, it issues from the decomposition and oxidation of the body as an organic compound, in union with a part of the carbon and hydrogen, and, in the case ot man, principally as urea. The amount of urea which can be formed from the proteid is about one-third of the weight of the proteid. In order therefore to ascertain the heat-equivalent of the proteid in our organism, we must deduct one-third of the heat-equivalent of urea from that of the proteid. But this figure would come out rather too high, because the nitrogen leaves our body not only as urea, but partly as a compound containing both more carbon and more hydrogen. We must therefore subtract at least 800 units of heat from the heat-equivalent of the proteids in the above table, and we then obtain figures which are only a little higher than those of the carbohydrates. As a store of energy in our bodies therefore, the carbohydrates are, in a quantitative respect, about equivalent to the proteids. The heat-equivalent of fats, on the other hand, is twice as great.

Little has as yet been ascertained as to the manner in which the organs, in the performance of their various functions, utilize the potential energy acquired with the food. As muscle consists chiefly of proteid, it was a plausible supposition that this substance was the source of muscular work. This view was maintained by Liebig, who contrasted the food-stuffs containing no nitrogen—the fats and carbohydrates—as "respiratory foods" with the proteids as "plastic foods." He taught that the former served mainly to generate heat. At the present time we know that, in muscular work, the excretion of nitrogen is increased only in a slight degree, but that the excretion of carbonic acid and the absorption of oxygen is notably increased; that therefore muscle works principally with material free from nitrogen. We know that a store of carbohydrates is to be found in the muscles in the form of glycogen, and that this store disappears during work. It thus appears that the carbohydrates serve as the chief sources of energy in muscle.[1] The fats and the carbohydrates may replace each other, but only within certain limits; they do not appear to play exactly the same part. This is proved by their simultaneous appearance

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[1] The question as to the source of muscular energy will be fully treated in Lecture XXIII.

in the milk of all carnivora, omnivora, and herbivora. It is further proved by the instinctive desire for the addition of fat to a diet, however abundant in carbohydrates it may be, and the desire, on the other hand, for the addition of carbohydrates to the richest fat-diet.

The fats are, at any rate, the most fertile sources of heat. Concerning the importance of animal heat in vital functions, we know, so far, that all chemical processes, as well as the interchange of energy connected with them, and the functions of the body dependent upon them, are more intense at a higher temperature. The fact that the functions of the nervous system, and of the muscles especially, are performed more rapidly at a higher temperature, may be easily demonstrated, as is well known, on poikilothermic animals.

It has not yet been ascertained which functions of the body are aided by the decomposition and oxidation of the large amount of proteid, which no other food-substance can replace. It is a matter of experience, that each person must be daily supplied with at least 100 grms. of proteid in one form or another. If he eats less than this amount, he must use part of the proteid of his tissues, however large a quantity of fat and carbohydrates he takes as well.[1] The fats and carbohydrates can only act in a certain degree as substitutes for the proteids.

We know indeed that the elements of our tissues which are rich in proteids undergo, like all unicellular organisms, a rapid change of generations; that increase, death of one part, growth and division of another, follow each other in uninterrupted succession. In the epidermis (the tissue most convenient for observation), we see the older cells continually dying off and being replaced by the proliferation of under layers. The same process has been traced in the epithelial cells of the intestine and of certain glands. A glance at a section of bone shows that newly-formed concentric lamellæ are continually growing into the older system as it becomes absorbed. We shall see, when we come to consider the processes of absorption in the intestine (Lectures XIII. and XV.), that the leucocytes also undergo rapid growth and destruction. Why should not the

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[1] From numerous experiments recently communicated, it appears that when a large amount of carbohydrates is taken, much less than 100 grms. of proteid is almost, if not quite, sufficient to maintain nitrogenous equilibrium. It is open to question however whether it would be so over a long period of laborious work and normal sexual life. *Vide* C. Voit, E. Voit und Constantinidi, *Zeitschr. f. Biolog.*, vol. xxv. p. 232: 1888; Hirschfeld, *Virchow's Arch.*, vol. cxiv. p. 301: 1888; and Pflüger's *Arch.*, vol. xlix. p. 428: 1889; and Muneo Kumagawa, *Virchow's Arch.*, vol. cxvi. p. 370: 1889. Compare also end of Lect. VIII.

same thing be taking place in the tissues hidden from our observation?

But the material of the dying cells may be used up in the growth of the surviving ones. The necessity for a daily consumption of 100 grms. of proteid is incomprehensible, so long as we do not know of any function of the body in the performance of which the chemical potential energies of the destroyed proteid are used up.

As we know for a fact that proteid is the only one of the three main groups of food that cannot be replaced by any other, our choice and combination of the articles of diet must be regulated by the amount of proteid they contain. In the following table[1] may be seen the average composition of the most important articles of diet, arranged according to the quantity of proteid found in them:—

TABLE I.

One Hundred Grms. of Food in a Natural State Contain—

	Proteid.	Fats.	Carbohydrates.
Apples	0.4	—	13
Carrots	1.1	0.2	9
Potatoes	2.0	0.1	20
Human milk	2.4	4.0	6
Cabbage (various)	3.3	0.7	7
Cow's milk	3.4	4.0	5
Rice	8.0	0.9	77
Maize	10.0	4.6	71
Wheat	12.0	1.7	70
Egg-albumin	13.0	0.3	—
Fat fish (eel)	13.0	28.0	—
Fat pork	15.0	37.0	—
Yolk of egg	16.0	32.0	—
Fat beef	17.0	26.0	—
Lean fish (pike)	18.0	0.5	—
Lean beef	21.0	1.5	—
Peas	23.0	1.8	58

TABLE II.

One Hundred Grms. of Dried Substances Contain—

	Proteid.	Fats.	Carbohydrates.
Apples	2.4	—	79
Potatoes	8.0	0.6	87
Rice	9.0	1.0	89
Carrots	10.0	2.0	82
Maize	11.0	5.0	81
Wheat	14.0	2.0	81
Human milk	18.0	30.0	48

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[1] The numbers are taken from the work of J. König, "Chemie der menschlichen Nahrungs- und Genussmittel," 2d edit. (Berlin, 1882), in which will be found an exhaustive collection of all former analyses.

TABLE II. (*continued*).

	Proteid.	Fats	Carbohydrates.
Cabbage	26.0	5.0	56
Peas	27.0	2.0	62
Cow's milk	27.0	29.0	38
Fat pork	28.0	71.0	—
Fat fish	30.0	67.0	—
Yolk of egg	33.0	65.0	—
Fat beef	39.0	59.0	—
Lean beef	89.0	6.0	—
Egg-albumin	89.0	2.0	—
Lean fish	90.0	2.5	—

In the following table we give the amount which it is necessary to eat of the various articles of diet in their natural undried condition, in order to convey 100 grms. of proteid into our bodies :—

TABLE III.

ONE HUNDRED GRMS. OF PROTEID ARE CONTAINED IN—

25,000	grms.	apples.	750	grms.	egg-albumin.
9000	"	carrots.	750	"	fat fish (eel).
5000	"	potatoes.	650	"	fat pork.
4200	"	human milk.	620	"	yolk of egg.
3000	"	cabbage.	600	"	fat beef.
3000	"	cow's milk.	550	"	lean fish.
1250	"	rice.	480	"	lean beef.
1000	"	maize.	430	"	peas.
800	"	wheat.			

In the following table we give the amount of dried articles of food which contain 100 grms. of proteid :—

TABLE IV.

ONE HUNDRED GRMS. OF PROTEID ARE CONTAINED IN—

4200	grms.	dried	apples.	370	grms.	dried	cow's milk.
1250	"	"	potatoes.	360	"	"	fat pork.
1100	"	"	rice.	330	"	"	fat fish.
1000	"	"	carrots.	300	"	"	yolk of egg.
900	"	"	maize.	250	"	"	fat beef.
700	"	"	wheat.	112	"	"	lean beef.
550	"	"	human milk.	112	"	"	egg-albumin.
440	"	"	cabbage.	110	"	"	lean fish (pike).
370	"	"	peas.				

If we subtract 100 from the numbers given, we learn from this last table how much of the other solid constituents, especially carbohydrates and fats, we must consume in order to obtain 100 grms. of proteid. In the following two tables these quantities are divided into carbohydrates and fats ; in Table V. they are arranged according to increase of carbohydrates, and in Table VI. according to increase of fats.

TABLE V.

WITH ONE HUNDRED GRMS. OF PROTEID WE TAKE UP IN—

	Carbohydrates.	Fats.
Cow's milk	140	107
Cabbage	220	21
Peas	230	7
Human milk	270	170
Wheat	580	14
Maize	740	46
Carrots	820	20
Rice	990	11
Potatoes	1000	8
Apples	3300	0

TABLE VI.

WITH ONE HUNDRED GRMS. OF PROTEID WE TAKE UP IN—

	Fats.	Carbohydrates.
Apples	—	3300
Egg-albumin	2	—
Pike	3	—
Lean beef	7	—
Peas	7	230
Potatoes	8	1090
Rice	11	990
Corn	14	580
Carrots	20	820
Cabbage	21	220
Maize	46	740
Cow's milk	107	140
Fat beef	150	—
Human milk	170	270
Yolk of egg	200	—
Eel	220	—
Fat Pork	250	—

In forming an opinion from these tables concerning the value of the different animal and vegetable foods, the following must also be taken into consideration. The amount of proteid in most articles of food has not been accurately determined. The amount of nitrogen only has been ascertained, and from this the amount of proteid has been calculated under the supposition that no other nitrogen-compounds exist in food, and that all kinds of proteids contain 16 per cent. of nitrogen. Both assumptions are wanting in precision. The amount of nitrogen in the various proteids varies, as we have seen, from 15 to 19 per cent. The other assumption, that foods contain no other nitrogen-compound, holds good in the case of the grains of cereals and leguminosæ. But in most of the other vegetable food-stuffs, ammonia, nitric acid, amides, amido-acids, &c., are found in considerable quantities. In certain kinds of vegetables the nitrogen of these compounds amounts to more than one-third of the total nitrogen.

It would also be a serious mistake to calculate the amount of proteid from the amount of nitrogen in meat. This contains a considerable quantity of gelatin-yielding substances which, as I have already pointed out, have a totally different action in nutrition to that of proteid. The collagenous substances of animal food may be regarded as more analogous to the carbohydrates of vegetable food than to the proteids. If therefore the nutrient value of meat and vegetables be judged from the above tables according to their relative amount of proteid, the value of the meat will be rated too highly, and that of the vegetables not highly enough.

On the other hand it must be remembered that animal food is much more completely absorbed than vegetable food. The capability of absorption of the proteid in different foods has of late been accurately tested by a careful comparison of the amount of nitrogen in the nutriment taken with that in the feces. It has thus been ascertained that the proteid of the meat almost entirely disappears. A considerable part of the proteid in milk reappears in the feces, and a still larger proportion is unabsorbed from vegetables. The table on p. 69 gives the results of these experiments on the absorption of proteid; they have all been carried out on human beings.

If the following table be compared with Tables III. and IV., it appears scarcely possible that a man could take up, in the form of vegetables, the daily amount of at least 100 grms. of proteid necessary to maintain nitrogenous equilibrium. The potato appears especially unsuited for this purpose; 5 kgrms. must be eaten in order to introduce 100 grms. of proteid into the stomach, but 7 kgrms. must be consumed to allow of the absorption of 100 grms. of proteid. English statisticians do in fact show that Irish workmen, who live chiefly on potatoes, eat on an average 4 to 6.5 kgrms. each daily. This appears scarcely credible. The person experimented on by Rubner,[1] a powerful soldier, who was accustomed to take large quantities of potato when at home in the Bavarian Alps, could not manage more than from 3 to 3.5 kgrms., although this monotonous form of food was prepared in various ways, with salt or with butter, with vinegar and oil as a salad, in the form of chips, or baked; and although the man was eating all day long. The potatoes he ate contained only 71.5 grms. of proteid, of which 23.1 grms. remained unabsorbed. He could not therefore maintain his nitrogenous equilibrium, as he gave out

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[1] Rubner, *loc. cit.*, vol. xv. p. 146.

Food.	Percentage of unabsorbed proteid.[1]	Author.
Beef (the same person being experimented on)	2.5 2.8	Rubner[2]
Eggs	2.9	Rubner
Milk and cheese (the same person)	2.9 4.9 3.7	Rubner
Milk[3] (four experiments on four different people)	6.5 7.0 7.7 12.0	Rubner
"Leguminose" (flour from leguminosæ and cereals)	8.2 10.5	Strümpell[4]
Macaroni	11.2	Rubner
Maize	15.5	Rubner
Peas and bread	12.0–20.0	Woroschiloff[5]
Vermicelli	17.1	Rubner
Savoy cabbage	18.5	Rubner
Wheat bread	19.9	Meyer[6]
Rice	20.4	Rubner
Rye bread	22.2	Meyer
White bread (the same person)	18.7 20.7 24.6 25.7	Rubner
Peas, shelled and well boiled (the same person)	17.5 27.8	Rubner
Broad beans, well cooked	30.25	Prausnitz[7]
Whole wheat-meal bread	30.5	Rubner
Black break (rye bread)	32.0	Rubner
Potatoes	32.2	Rubner
Harsford-Liebig bread	32.4	Meyer
Carrots (boiled)	39.0	Rubner
Lentils	40.0	Strümpell
Bran bread	42.3	Meyer
Rye-bran bread	45.4	Huldgren and Landergren[8]
Lentils, potatoes, and bread	53.5	Hofmann[9]

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[1] These figures are rather too high, because the nitrogen in the feces is contained, not only in the unabsorbed food, but also in the products of metabolism, which are eliminated in the intestine. According to Rieder's experiments with non-nitrogenous food, the nitrogen eliminated in the intestine amounts to 8 per cent. of the total nitrogen excreted under these circumstances. *Zeitschr. f. Biolog.*, vol. xx. p. 478: 1884.

[2] Max Rubner, *Zeitschr. f. Biolog.*, vol. xiv. p. 115: 1879; vol. xvi. p. 119 1880; vol. xix. p. 45: 1883.

[3] Concerning the absorbability of milk, see W. Prausnitz, *Zeitschr. f. Biolog.*, vol. xxv. p. 533: 1889.

[4] A. Strümpell, *Deutsch. Arch. f. klin. Med.*, vol. xvii. p. 108: 1876.

[5] Woroschiloff, Botkin's *Arch.*, vol. iv. p. 1: 1872 (Russian). Unfortunately a very inaccurate account of this useful work is to be found in the *Berl. klin. Wochenschr.*, p. 90: 1873.

[6] G. Meyer, *Zeitschr. f. Biolog.*, vol. vii. p. 1: 1871.

[7] W. Prausnitz, *Zeitschr. f. Biolog.*, vol. xxvi. p. 227: 1890.

[8] E. Huldgren and E. Landergren, *Nord. Med. Arkiv*, p. 21: 1890.

[9] Fr. Hofmann, "Die Bedeutung der Fleischnahrung und Fleischconserven," pp. 11, 44: Leipzig, 1880.

more nitrogen through the kidneys than he absorbed from the intestines, thus using up the store of proteid in his tissues, *i. e.*, he was gradually dying of hunger. A sceptical observer must, however, concede the possibility that many Irish laborers may consume 5 kgrms. of potatoes and maintain their nitrogenous equilibrium. The difference in individuals is of course very great.

I wish further to point out that such a diet can be better borne by adults than by children. Children have to build up an organism rich in proteid; adults have only to maintain the previous store, performing their muscular work with the carbohydrates, of which a superfluity is introduced with a potato-diet. The frightful mortality among children of the lower classes is perhaps largely due to the want of proteid in their food.

Among the more important articles of vegetable food, the leguminosæ contain the largest amount of proteid. A diet of these, if properly prepared, maintains nitrogenous equilibrium. This is shown by the experiments Woroschiloff[1] made upon himself. He lived for thirty days entirely upon peas, bread, and sugar, while at the same time he performed 8528 kilogrammeters of work per hour, for the space of one to three hours a day, and yet he showed no loss of proteid. The person whom Rubner[2] experimented upon, also kept his nitrogenous equilibrium on a diet of peas.

If an exclusively vegetable diet proves insufficient, it is perhaps caused less by the want of proteid than by the want of fat. If we glance at Table V. (p. 67), we see that the relation of carbohydrates to proteid is the same in a diet of leguminosæ and cereals as in milk, with the difference that the former contain much less fat than milk does. We should hence *à priori* expect to find that a man could exist very well upon cereals and leguminosæ, with the addition of fat, or perhaps even upon cereals and fat only. Milk is the normal food of the infant, not of the adult. The adult requires, as I have just explained, relatively less proteid and more carbohydrates. We might, therefore, conclude that the normal food of the adult would be furnished by the proteid and carbohydrates, in the proportion met with in the cereals, and that this diet would only require the addition of fat. This theory appears to be confirmed by experience. The laborers in some districts of Bavaria, who do the hardest work, are said to live upon a diet prepared from flour and lard.[3] This mode of living would

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[1] Woroschiloff, *loc. cit.*

[2] Rubner, *loc. cit.*, vol. xvi. p. 125: 1880.

[3] H. Ranke, "Die bayr. Landwirthschaft in den letzten 10 Jahren." Festgabe, &c., p. 160: München, 1872; Liebig, *Sitzungsber. d. bayr. Akad.*, vol. ii. p. 463: 1869; "Reden und Abhand.," p. 121. Compare also Ohlmüller, *Zeitschr. f. Biolog.*, vol. xx. p. 393: 1884.

be the ideal of vegetarians[1] if the fat were likewise obtained from the vegetable kingdom, in the form of oil, olives, nuts, cocoa. From investigations made by Panum and Buntzen, it appears that even a carnivorous animal can be nourished on cereals and fat; a dog which was fed exclusively on groats and butter could be kept in good health for two months without loss of weight.[2] Unfortunately this experiment lasted much too short a time.

The fat of all food is very completely absorbed,[3] far more so than the proteids. The same is true of all carbohydrates,[4] with the single exception of cellulose. This was held to be totally indigestible until quite recently, when it was proved by experiments on ruminants[5] at the farm-stations kept for investigations, that from 60 to 70 per cent. of the woody fibers disappear from the digestive canal. At the experimental farm of Tharand,[6] it was even found that from 30 to 40 per cent. of the cellulose of sawdust and paper was absorbed by sheep when mixed and eaten with hay. Weiske[7] was the first to make experiments on human beings, which he carried out on himself and on another person. He found that one of them digested 62.7 per cent., the other 47.3 per cent., of the woody fibers in the food, which consisted of carrots, cabbage, and celery. Later on Knieriem[8] made experiments on himself, and found that he digested 25.3 per cent. of the tender woody fibers of lettuce, but only 4.4 per cent. of the tougher fibers of Scorzonera. The latter figure is within the limits of unavoidable error. How cellulose undergoes solution in the intestines, we shall explain further on, when we come to the consideration of the digestive processes.

Cellulose can scarcely be classed among the food-substances of human beings. On the other hand it is of great importance in acting as a mechanical stimulus to promote the peristalsis of the intestine. For this reason cellulose is absolutely essential to animals with a long intestinal tract. If rabbits are fed on a

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[1] I have published a detailed criticism of vegetarianism in a small pamphlet, "Der Vegetarianismus" (Berlin, Hirschwald: 1885).

[2] *Jahresbericht über die Fortschritte der Thierchemie*, vol. iv., of the year 1874, p. 365: Wiesbaden, 1875.

[3] Rubner, *loc. cit.*, vol. xv. p. 189.

[4] Rubner, *loc. cit.*, p. 192.

[5] Haubner, *Zeitschr. für Landwirthschaft*, p. 177: 1855; Henneberg and Stohmann, "Beiträge zur Begründung einer rationellen Fütterung der Wiederkäuer," Heft i.: 1860; Heft ii.: 1863.

[6] "Der chemische Ackersmann," pp. 51, 118: 1860.

[7] H. Weiske, *Zeitschr. f. Biolog.*, vol. vi. p. 456: 1870.

[8] v. Knieriem, "Ueber die Verwerthung der Cellulose im thierischen Organismus," Festschrift: Riga, 1884. Also printed in the *Zeitschrift f. Biolog.*, vol. xxi. p. 67: 1885.

diet containing no cellulose, the onward movement of the intestinal contents ceases, inflammation in the intestines ensues, and the animals rapidly die. But if horn-parings be added to the same food, nutrition is normal.[1] These horn-parings are, as Knieriem proved by experiments devoted to that purpose, absolutely undigested, and can therefore only have taken the place of woody fiber in so far as its mechanical properties were concerned. Of three mice, fed entirely on milk, one died after forty-seven days of intussusception, as dissection showed.[2]

The following are the details of a post-mortem examination of a rabbit which had died for lack of cellulose: "The stomach only contained mucus, and showed signs of incipient inflammation in the region of the pylorus; the small intestine, full of mucus, was much inflamed throughout its whole length, as was also the cecum. The latter was largely filled with excrement of the consistency of putty, which adhered firmly to the walls and folds of the cecum. The difference between these contents and those of the cecum of a normally fed rabbit is very noticeable, for here the mass in the cecum is pretty loose, falling almost completely away if the intestine be bent backwards, and this loose consistency is caused only by the tough fibers, by means of which the communication between the anus and the stomach is kept open. This could hardly have been the case in the animal which died."[3]

The short intestine of carnivora does not require a mechanical stimulus to produce peristaltic action. The intestine of human beings is well known to be of medium length; a man's life therefore is not endangered by deprivation of cellulose, although the normal movement of the intestine might be thereby impeded. The muscular wall of the intestine becomes atrophied like every other muscle, if it has no work to do. We must therefore see that the diet of human beings does not lack woody fibers. The excessive fear of indigestible food which prevails among the wealthier classes may lead to universal debility of the intestinal muscular walls. Habitual constipation would perhaps not be such a common trouble if we were accustomed from our childhood to a dietary containing a sufficient supply of woody fiber. Of late years whole-meal bread, which is rich in cellulose, has been a successful remedy for chronic constipation. It is well known that an exclusive milk diet may occasion constipation.

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[1] Knieriem, *loc. cit.*, pp. 6, 17–19.

[2] N. Lunin (Bunge's laboratory), "Ueber die Bedeutung der anorganischen Salze für die Ernährung des Thieres," p. 15, Dissert.: Dorpat, 1880. Also printed in the *Zeitschr. f. physiol. Chem.*, vol. v. p. 37: 1881.

[3] Knieriem, *loc. cit.*, p. 17.

On the other hand it is urged that the rapid and continual movement of the intestinal contents in consequence of the irritating action of the woody fibers has one drawback—the incomplete utilization of the food. In fact, Meyer[1] has already shown, by direct experiment, that it is more economical to feed on the dearer bread of fine flour than on the cheaper bran bread. Fr. Hofmann showed that the addition of cellulose diminishes the nutritive value of meat.[2] At the same time, it appears to me that the advantages of food containing cellulose far outweigh the drawbacks.

The following table shows the amount of cellulose contained in the most important vegetables used as food by man ; from a dietetic point of view this is not without interest.

PERCENTAGE OF CELLULOSE IN VARIOUS ARTICLES OF DIET IN A NATURAL STATE.[3]

	Cellulose.	Water.
Rice flour	0.2	13.0
Wheat flour (fine)	0.3	13.0
Cucumber	0.6	96.0
Rice	0.6	13.0
Onion	0.7	86.0
Potato	0.8	75.0
Cauliflower	0.9	91.0
Asparagus	1.0	94.0
Carrots	1.0	89.0
Melon	1.1	90.0
Mushroom	1.4	91.0
Apple (including pips)	1.5	85.0
Rye meal	1.6	14.0
Radish	1.6	87.0
Cabbage	1.8	90.0
Green peas	1.9	78.0
Rye	2.0	15.0
Strawberries	2.3	88.0
Maize	2.5	13.0
Wheat	2.5	14.0
Peas	2.6	15.0
Horseradish	2.8	77.0
Lentils	3.0	12.0
Hazel-nut	3.3	3.8
Beans	3.6	14.0
Grapes (including pips)	3.6	78.0
Pears (including pips)	4.3	83.0
Barley	5.3	14.0
Walnut	6.2	4.7
Almonds	6.6	5.4
Raspberries	6.7	86.0

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[1] G. Meyer, *Zeitschr. f. Biolog.*, vol. vii. pp. 32 and 33: 1871; compare also Rubner, *Zeitschr. f. Biolog.*, vol. xix. p. 45: 1883.

[2] Voit, *Sitzungsber. der bayr. Akad.:* December, 1869.

[3] The average figure, taken from König's work previously quoted.

PERCENTAGE OF CELLULOSE IN DRIED ARTICLES OF DIET.

	Cellulose.		Cellulose.
Rice flour	0.2	Spinach	8.1
Wheat flour (fine)	0.4	Green peas	8.7
Rice	0.7	Carrot	8.8
Rye meal	1.8	Apples	10.0
Rye	2.4	Radish	12.0
Wheat	2.9	Horseradish	12.0
Maize	2.9	Cauliflower	13.0
Potato	3.1	Cucumber	14.0
Hazel-nut	3.4	Mushroom	16.0
Lentils	4.1	Asparagus	17.0
Beans	4.1	Cabbage	18.0
Onion	5.0	Strawberries	19.0
Barley	6.2	Melon	22.0
Peas	6.4	Pears	25.0
Walnut	6.5	Raspberries	47.0
Almond	6.9		

The amount of carbohydrates and fats required for our daily nutrition cannot be determined, as they may either replace each other or be replaced by proteid. Experience has taught us that workingmen, who are able to obtain sufficient food, eat daily from 50 to 200 grms. of fat, and from 300 to 800 grms. of carbohydrates, besides from 100 to 150 grms. of proteid. Tables V. and VI. (p. 67) show us how we can combine such articles of nutrition in the most varied ways. The food must be more abundant in carbohydrates in proportion to the work performed by the muscles, and more abundant in fat according to the lowering of the surrounding temperature. Travellers in the far north relate that they were glad to adopt the habit, prevalent among the natives in those regions, of eating a pound of butter or oil in the day, and that the distaste for large quantities of fat returned as soon as they reached warmer climates. On the other hand the negroes in the plantations of the tropics, while doing the hardest muscular work, thrive on a dietary poor in fat, but very rich in carbohydrates.

LECTURE VI

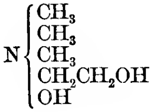
THE ORGANIC FOOD-STUFFS (*conclusion*)—THE ORGANIC COMPOUNDS OF PHOSPHORUS—CHOLESTERIN

In the previous chapters we have become acquainted with those organic substances which, according to the doctrines of physiology now prevailing, are requisite for the nutrition of man. But they are probably much more numerous.

Certain PHOSPHORUS COMPOUNDS should also probably be regarded as essential organic food-substances of man. In all animal and vegetable tissues, in every cell we find two complex organic compounds, which are very rich in phosphorus, the LECITHINS and the NUCLEINS.

The LECITHINS are compounds which we may regard as having been formed from the union of one molecule of glycerin with two molecules of a fatty acid (stearic acid, palmitic acid, or oleic acid) one molecule of phosphoric acid and one molecule of cholin, with the loss of four molecules of water.[1]

Cholin is an ammonium base, the composition of which is accurately known. When heated, it splits up into glycol (ethylene alcohol) and trimethylamin. Its synthesis corresponds with this decomposition: Wurtz[2] produced it by the action of ethylene oxide and water on trimethylamin. The formula of cholin is therefore—



$$N\begin{cases}CH_3\\CH_3\\CH_3\\CH_2CH_2OH\\OH\end{cases}$$

In the animal kingdom cholin has, up to the present time,

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[1] *Vide* Diakonow, *Centralbl. f. d. med. Wissensch.*, Nos. 1, 7, 28: 1868. Hoppe-Seyler, *Med. chem. Unters.*, Heft ii. p. 221: 1867; and Heft iii. p. 405: 1868; Strecker, *Ann. Chem. Pharm.*, vol. cxlviii. p. 77: 1868; Hundeshagen, "Zur Synthese des Lecithins," Inaug. Dissert.: Leipzig, 1883; E. Gilson, *Zeitschr. f. physiol. Chem.*, vol. xii. p. 585: 1888.

[2] Wurtz, *Ann. Chem. Pharm.*, Suppl. vi. pp. 116, 197: 1868. *Compt. rend.*, vol. lxv. p. 1015: 1867; and vol. lxvi. p. 772: 1868. Compare Baeyer, *Ann. Chem. Pharm.*, vol. cxl. p. 306: 1866; and vol. cxlii. p. 322: 1867.

been found only in lecithin. It was first obtained by Strecker[1] from the bile, which contains lecithin, and hence it was called cholin. Liebreich[2] found it among the products of decomposition of phosphorus compounds from nerve substance (brain). Diakonow showed that it was a product of decomposition of lecithin. In the tissues of plants cholin is found in other combinations as well as in lecithin. In mustard seed there is an alkaloid (sinapin) which, on boiling with alkalies, is resolved into sinapic acid and cholin. Two alkaloids have been obtained by Schmiedeberg and his pupils[3] from the fly-fungus (*Amanita muscaria*)—amanitin and muscarin, the former of which was found to be identical with cholin. The latter, a violent poison, differs from amanitin only in possessing one more atom of oxygen. In fact, by the action of boiling nitric acid on cholin (the cholin being taken indifferently from amanita, from the lecithin of the brain or of yolk of egg, as well as that synthetically produced), an alkaloid containing one more atom of oxygen was successfully obtained, which acted poisonously in a similar manner to muscarin; the action on the heart in particular being alike in both cases. This intimate connection between a substance contained in every animal and vegetable cell and a powerful poison, is a fact of great interest. According to the more recent researches of Boehm,[4] however, the muscarin artificially produced by oxidation of cholin is not identical with the muscarin from the fly-fungus, but is isomeric; the pharmacological action is different. Boehm found cholin in other fungi, and obtained it in large quantities from the residue of crushed cotton seeds and beech-nuts.

Lecithins have, in common with fats to which they are so nearly allied in composition, the property of solubility in alcohol and ether; they are also miscible in every proportion with fats; but at the same time they have the power of swelling and becoming slimy in water. For this reason they appear peculiarly adapted to aid in the interaction of watery solutions and substances not soluble in water, and to take part in the most various chemical processes in the tissues. But at present we know absolutely nothing about the part which the lecithins may play in any of the vital functions.

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[1] Strecker, *Ann. Chem. Pharm.*, vol. cxxiii. p. 353: 1862: vol. cxlviii. p. 76: 1868.

[2] Liebreich, *ibid.*, vol. cxxxiv. p. 29: 1865.

[3] Schmiedeberg and Koppe, "Das Muskarin, das giftige Alkaloid des Fliegenpilzes": Leipzig, 1869; E. Harnack, *Arch. f. exper. Path. u. Pharm.*, vol. iv. p. 168: 1875; Schmiedeberg and Harnack, *Arch. f. exper. Path. u. Pharm.*, vol. vi. p. 101: 1876.

[4] Boehm, *Arch. f. exper. Path. u. Pharm.*, vol. xix. p. 87: 1885.

The next question which must occupy our attention is whether the lecithins of our tissues are produced from the lecithins of food, or by synthesis from other materials such as fat, proteid, and phosphoric acid. It has been ascertained from experiments in Hoppe-Seyler's laboratory [1] that, in artificial pancreatic digestion, the lecithins take up water and readily split up into glycerin-phosphoric acid, fatty acids, and cholin. It is not yet known whether this decomposition is complete in the case of normal digestion, or whether a portion is absorbed undecomposed, and if so how large a portion; whether only the undecomposed part, when absorbed, can be utilized in the building up of the tissues, or whether the products of decomposition which are absorbed again become united; whether finally lecithin may also be formed from other material. The absorption of lecithin or of its products of decomposition is in any case complete; neither lecithin nor glycerin-phosphoric acid can ever be found in the feces. The presence of lecithin in milk [2] seems to show how essential that substance is in nutrition.

The generic name of NUCLEIN [3] has been bestowed upon a large number of very different organic phosphorus compounds, which are to be found in all animal and vegetable tissues, being especially abundant in the nuclei of cells. The nucleins have as yet been little investigated, and we have no proof that the pure substances hitherto isolated are chemical individuals. All are alike in being insoluble in alcohol, ether, water, and dilute mineral acids, and in being soluble in alkalies. The nucleins are acids. The phosphorus is given off from them all as phosphoric acid on boiling with water, and more rapidly so on boiling with alkalies or acids. But the organic substances which are combined with the phosphoric acid appear to be of very varying character, and have been but little investigated. Most nucleins are proteid compounds, although a few do not contain proteid. Many, on splitting up, produce xanthin, hypoxanthin, guanin, and adenin [4]—crystalline compounds rich

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[1] S. Bókay, *Zeitschr. f. physiol. Chem.*, vol. i. p. 157: 1877.

[2] Tolmatscheff, Hoppe-Seyler's *Med. chem. Unters.*, Heft ii. p. 272: 1867.

[3] The nucleins were first discovered and investigated by Miescher in the nuclei of pus-corpuscles, and subsequently in the yolk of egg and salmon-sperm (Hoppe-Seyler's *Med. chem. Unters.*, Heft iv. pp. 441, 502: 1871; *Verhandlungen der naturforschenden Gesellschaft zu Basel*, vol. vi. p. 138: 1874). The most recent and complete experiments on nucleins were made by Kossel *Zeitschr. f. physiol. Chem.*, vol. iii. p. 284: 1879; vol. iv. p. 290: 1880; vol. v. pp. 152, 267: 1881; "Untersuchungen über die Nucleine": Strassburg, 1881; *Zeitschr. f. physiol. Chem.*, vol. vi. p. 422: 1882; vol. vii. p. 7: 1882; vol. x. p. 250: 1886; vol. xii. p. 241: 1888; *Arch. f. Anat. u. Physiol.*, p. 181: 1891.

[4] Piccard, *Ber. d. deutsch. chem. Ges.*, vol. vii. p. 1714: 1874.

in nitrogen, which we shall describe more at length when we consider the chemistry of urine. The preparations of nuclein, hitherto analyzed, contained from 3.2 to 9.6 per cent. of phosphorus.

The nucleins have much the same solubilities as proteids, and are found united with these in the same morphological structures, but they can be separated by artificial gastric digestion (Lectures X. and XI.): the proteids are peptonized; the nucleins on the other hand are little affected by the gastric juice. It appears that the nucleins mostly occur in the tissues, not in a free state, but as compounds with proteid (nucleo-albumins), and perhaps also with lecithin, and that gastric digestion separates them from these bodies.

As an example of the percentage composition of nucleins, I may give the following analyses of preparations, which were to some extent pure. Since the nucleins have not yet been prepared in a crystalline state, we have no adequate guarantee of their chemical individuality or of the purity of the preparations.

	NUCLEINS PREPARED FROM—			
	Yeast.[1]	Yolk of Egg.[2]	Carp-Roe.[3]	
			I.	II.
C	40.8	42.1	48.0	47.8
H	5.4	6.1	7.2	7.2
N	16.0	14.7	14.7	12.7
S	0.4	0.55	0.3	—
P	6.2	5.19	2.4	2.9
Fe	—	0.29	—	0.25
O	31.3	31.05	—	—

From some of the nucleins the phosphoric acid may be split off in combination with part of the organic radical as an acid containing nitrogen, but free from sulphur, which, following Altmann's suggestion,[4] we may designate nucleic acid. As example of such an acid may be cited the nucleic acid split off from the nuclein of yeast, to which the formula $C_{40}H_{59}N_{16}O_{22}$, $2P_2O_5$ has been given.[5]

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[1] Kossel, *Zeitschr. f. physiol. Chem.*, vol. iii. p. 284 : 1879.

[2] Bunge, *ibid.*, vol. ix. p. 56 : 1885.

[3] G. Walter, *ibid.*, vol. xv. p. 489 : 1891.

[4] R. Altmann, Du Bois' *Arch.*, p. 524 : 1889.

[5] Altmann, *loc. cit.*

In certain cells nucleic acid appears to occur in a free state. Thus Miescher[1] has prepared a nucleic acid from salmon-sperm, to which he has assigned the formula $C_{40}H_{54}N_{14}O_{17}$, $2P_2O_5$. In the heads of the spermatozoa this acid is combined with the organic base, protamin (see Lecture XIX.), to form a salt. In the dried heads of the spermatozoa the nucleic acid amounts to 60.7 per cent. and the protamin to 19.8 per cent.

Whether the nucleins of our tissues arise from the nucleins of food (in which case the nucleins would rank among the number of essential food-substances), or whether the nucleins are formed in the body by synthesis, is a question of great importance, about which as little is known as concerning the mode in which the lecithins originate. The occurrence of nucleins in milk[2] seems to point to the former supposition as the correct one, whereas the slight digestibility of the nucleins would lead us to the latter conclusion. The experiments carried out in Hoppe-Seyler's laboratory[3] showed that nuclein is as little affected by artificial pancreatic, as by artificial gastric, digestion. Nuclein was found in abundance in the feces of dogs. A quantitative determination of the comparative amounts of nuclein in food and in the feces has not yet been made, and it is therefore not yet known whether the nucleins are absolutely indigestible, or whether a part, and if so how much, is absorbed.

The following observation, made by Miescher[4] on Rhine salmon, seems to show that the nucleins as well as the lecithins arise in the animal body by synthesis. The salmon travel up the river every year from the sea to spawn in the Upper Rhine. During the journey, the ovary grows from 0.4 to 19.27 per cent. of the salmon's entire weight. These journeyings last from four to fourteen weeks. During the whole of this time they take no food; the intestinal canal is always found empty. The material which goes to form the ovaries can only be produced by the muscles, which constitute the bulk of the fish's weight. Miescher showed by comparative determinations, made on fish of equal size, that the muscles

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[1] Miescher, *Arch. f. exp. Path. u. Pharm.*, vol. xxxvii. p. 100 : 1896.

[2] Nuclein was proved to be a constituent of milk by Lubavin (Hoppe-Seyler's *Med. chem. Unters.*, Heft iv. p. 463 : 1871; *Ber. d. deutsch. chem. Ges.*, vol. x. p. 2237 : 1877; and vol. xii. p. 1021 : 1879). Hammarsten showed that nuclein is contained in milk as nucleo-albumin (*Zeitschr. f. physiol. Chem.*, vol. vii. p. 227 : 1883).

[3] Bókay, *Zeitschr. f. physiol. Chem.*, vol. i. p. 157 : 1877.

[4] Miescher, "Statistische u. biologische Beiträge zur Kenntniss vom Leben des Rheinlachses," Separatabdruck aus der schweizerischen Literatursammlung zur internationalen Fischerei-Ausstellung in Berlin, p. 183 : 1880; and *Arch. f. Anat. u. Physiol.*, Anat. Abth., p. 193 : 1881.

disappear in proportion as the ovaries develop, and that the loss in weight of the large lateral trunk-muscles is sufficient to cover the increase in weight of the ovaries. Now the ova are very rich in lecithin and nuclein; the muscles however are poor in these compounds. But the muscles contain phosphoric acid in abundance in another form, probably as potassium salts, loosely united with proteids. Miescher therefore concludes that the new compounds characteristic of the egg are formed from the proteid, the fat, and the phosphates of the muscles, a profound chemical rearrangement taking place.

Perhaps CHOLESTERIN also belongs to the organic food-stuffs essential to man. Like the lecithins and nucleins, it is a normal constituent of all vegetable and animal tissues and of milk.[1] Here also we do not know whether cholesterin is formed only in the plant, and enters the animal body either directly in the form of vegetable food (in the case of herbivora), or indirectly (in the case of carnivora), or whether it is formed from other material in the animal body. Cholesterin is, like lecithins and fats, insoluble in water, and soluble in ether and alcohol, but is distinguished from them by its insolubility in boiling potash; it cannot be saponified, as it is not an ethereal salt, but a monatomic alcohol with the composition $C_{27}H_{45}OH$. The chemical constitution of this compound is not known.

We are still in complete ignorance concerning the fate of cholesterin in the organism. Considerable quantities of cholesterin are being continually turned out into the intestine along with the bile, but we do not know whether this cholesterin is taken up preformed in the food or whether it is formed from other substances by the organism itself. In human feces cholesterin occurs modified as dihydrocholesterin, formed by the addition of two atoms of hydrogen to the unsaturated cholesterin molecule. This reduction product was named by its discoverer, Bondzynski,[2] koprosterin, and assigned the formula $C_{27}H_{47}OH$. That this process of reduction takes place in the intestine is rendered probable by the fact that in dogs, with their short gut, the cholesterin of the food and of the bile is passed unchanged, whereas in the long intestine of the horse, cholesterin undergoes a still further reduction, appearing in the feces as $C_{27}H_{53}OH$. It has not yet proved possible, outside the body, by means of reducing or putrefactive processes, to prepare the koprosterin from cholesterin. Koprosterin

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[1] Tolmatscheff, Hoppe-Seyler's *Med. chem. Unters.*, Heft ii. p. 272: 1867; and Schmidt-Mülheim, Pflüger's *Arch.*, vol. xxx. p. 384 : 1883.

[2] St. Bondzynski, *Ber. d. deutsch. chem. Ges.*, p. 476 : 1896; Bondzynski and Humnicki, *Zeitschr. f. physiol. Chem.*, vol. xxii. p. 396 : 1896.

differs from cholesterin both in its melting-point and in its action on polarized light, being dextro-rotatory, while cholesterin is levo-rotatory. Moreover the color-reactions of koprosterin differ from those of cholesterin.

We know nothing as yet concerning the significance of cholesterin for any vital functions.

LECTURE VII

THE INORGANIC FOOD-STUFFS

In our previous remarks on alimentary substances we have not given any account of the inorganic materials, salts and water.

In deciding the question of man's need for inorganic salts, we must clearly distinguish between the growing and the adult body. It is evident that the former requires a considerable amount of inorganic salts for its development. The quality and quantity needed may be best seen from the composition of milk. An infant weighing 6 or 7 kgrms.[1] takes about a liter of milk daily. This contains—[2]

K_2O	0.78	grm.
Na_2O	0.23	"
CaO	0.33	"
MgO	0.06	"
Fe_2O_3	0.004	"
P_2O_5	0.47	"
Cl	0.44	"

It would be very interesting to compare the composition of the ash of milk with that of the total ash of the infant. But unfortunately no analysis of the total ash of an infant has ever been made. A comparative analysis of the ash of dog's milk and the total ash of a sucking puppy resulted in the following figures,[3] which I give together with the analysis of the ash of blood, and another of the total ash of a young rabbit and a kitten while being suckled :—

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[1] This is what an infant usually weighs in the sixth month. I choose this stage for the above table, because the numbers are of a suitable size. Assuming that the need for inorganic salts is in proportion to the body-weight, the decimal point has only to be moved one figure to the right, in order to ascertain the amount required by an adult. But these figures can only be taken as a maximal value. As we shall see it is probable that the adult does not require nearly so large an amount of inorganic salts.

[2] G. Bunge, *Zeitschr. f. Biolog.*, vol. x. p. 316: 1874.

[3] Bunge, *loc. cit.*, p. 326; and Du Bois' *Arch.*, p. 539: 1886.

One hundred parts of ash contain.	Sucking young of animals.			Dog's milk.	Dog's blood.	Dog's blood serum.
	Rabbit.	Dog.	Cat.			
K_2O	10.8	8.5	10.1	10.7	3.1	2.4
Na_2O	6.0	8.2	8.3	6.1	45.6	52.1
CaO	35.0	35.8	34.1	34.4	0.9	2.1
MgO	2.2	1.6	1.5	1.5	0.4	0.5
Fe_2O_3	0.23	0.34	0.24	0.14	9.4	0.12
P_2O_5	41.9	39.8	40.2	37.5	13.3	5.9
Cl	4.9	7.3	7.1	12.4	35.6	47.6

This table shows the remarkable fact that the proportion of the various inorganic substances to each other in milk, is almost the same as it is in the whole body of animals while they are being suckled. This correspondence is the more remarkable as the quantitative composition of the inorganic residue of blood is completely different. But the epithelial cells of the mammary gland do not derive their nourishment directly from the blood, but from the lymph which has transuded from the latter; and the composition of the ash of lymph differs much more. The fact that the ash of milk contains more potassium and less sodium than the total ash of the suckling may be teleologically explained by the fact that, as I have proved by a series of analyses,[1] the animal as it grows always becomes richer in potassium and poorer in sodium; this probably depends on the relative increase of the muscles which contain an abundance of potassium, and the relative diminution of the cartilage which is rich in sodium. The larger amount of chlorin in milk may perhaps be explained by the fact that the chlorids are useful, not only in the construction of the organs, but also in the preparation of the digestive secretions, and that those chlorids which have reached the intestine with the digestive secretions do not again become completely absorbed. It appears also that the chlorids are important for renal secretion. The nitrogenous products of metabolism cannot be eliminated simply in the form of aqueous solutions; the presence of chlorids is also necessary.[2] This is shown by the fact, among others, that diuretics also increase the excretion of chlorin.

It follows that the inorganic constituents are all appropriated by the epithelial cells of the mammary gland from the

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[1] Bunge, *loc. cit.*, p. 324.

[2] The chlorids are occasionally absent from the urine in certain febrile diseases, especially in pneumonia. See Lecture XXVIII.

blood-plasma (which is of a totally different composition), in the exact proportion required by the young animal for its development into an organism like that of the parent.

This fact alone refutes all previous attempts at a mechanical explanation of the activity of the glands. It cannot be objected that the secretion of milk does not correspond with the composition of the sucking animal, but, on the contrary, that the tissues of the latter are built up in accordance with the composition of the milk; for the incinerated puppies were only four days old, and were therefore born with an ash of a composition corresponding to that of the ash of the milk. We also find a similar composition of the total ash as far down as the lower vertebrates, which have no mammary glands.

We now know exactly what salts are required by the growing animal, and in what proportion each must be introduced. We may now therefore ask whether the child, in passing from milk to another form of diet, will continue to obtain these inorganic salts in sufficient quantities. In answer to this question, I give the following table containing the most reliable determinations of the constituents of the ash of the most important articles of diet, together with analyses of the ash of milk. The articles of diet are arranged according to the ratio of LIME contained:—

IN ONE HUNDRED PARTS OF DRIED SUBSTANCE THE PROPORTIONS ARE—

	K_2O.	Na_2O.	**CaO.**	MgO.	Fe_2O_3.	P_2O_5.	Cl.[1]
Beef	1.66	0.32	**0.029**	0.152	0.02	1.83	0.28
Wheat	0.62	0.06	**0.065**	0.24	0.026	0.94	(?)
Potato	2.28	0.11	**0.100**	0.19	0.042	0.64	0.13
Egg-albumin	1.44	1.45	**0.130**	0.13	0.026	0.20	1.32
Peas	1.13	0.03	**0.137**	0.22	0.024	0.99	(?)
Human milk	0.58	0.17	**0.243**	0.05	0.003	0.35	0.32
Yolk of egg	0.27	0.17	**0.380**	0.06	0.040	1.90	0.35
Cow's milk	1.67	1.05	**1.51**	0.20	0.003	1.86	1.60

The above table shows that the other articles of food possess all the inorganic constituents in as large or in a larger quantity than milk. LIME is the only inorganic material which we have to provide for in the choice of a child's food. If brought up on meat and bread a child would probably not obtain the lime requisite for the growth of its frame. The leguminosæ contain more; but the only food which has the same amount

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[1] The amount of chlorin in cereals and leguminosæ has never yet been correctly determined, too low an estimate having been formed. Concerning this, see Behaghel von Adlerskron, *Zeitschr. f. analyt. Chem.*, vol. xii.: 1873.

as milk is the yolk of egg, which should therefore always be given to children when milk is either not procurable or cannot be digested. Considerable quantities of lime occur in spring-water, but it is not known whether these are assimilated. Lime is found combined with organic substances in food; it is therefore irrational to prescribe lime for children in the form of inorganic compounds. In medical practice, rickety children are constantly being ordered a couple of teaspoonfuls of lime-water. This is useless, because the amount ordered is far too small. A saturated solution of lime contains less lime than cow's milk. In a pint of cow's milk I found 1.7 grm. CaO; a pint of lime-water contains only 1.3 grm. CaO.

The nature and causes of rickets are still quite unknown. It is a fact that artificial feeding of growing animals on a diet containing a little lime can produce a diminution of the salts of lime in the bones, rendering them abnormally pliable and brittle. It is also affirmed that in several experiments of this nature true rickets has been produced with all the characteristics of this disease.[1] But it is equally a fact that children become rickety who have never suffered from want of lime in their food. In these cases it seems obvious to suppose that, owing to disturbed digestion, the lime salts have not been adequately absorbed;[2] or that, in spite of adequate absorption, they have not been assimilated owing to abnormal processes in the bone-forming tissues. All speculation on the truth of either theory is quite useless, until we have careful and reliable experiments on the metabolism of rickety children compared with that of healthy ones of the same age, and brought up on the same food. In spite of much experimental work on the subject, all attempts to give a satisfactory explanation of the causation of osteomalacia have been as unsuccessful as in the case of rickets.[3]

Finally, the above table shows that cow's milk, compared with organic food-stuffs, is much richer in inorganic salts than

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[1] Erwin Voit, *Zeitschr. f. Biolog.*, vol. xvi. p. 55: 1880. An account of the previous literature will also be found here. See further, A. Baginsky, Virchow's *Arch.*, vol. lxxxvii. p. 301: 1882; and Seemann, *Zeitschr. f. klin. Med.*, vol. v. pp. 1, 152: 1882.

[2] In the researches on the absorbability of calcium compounds we meet with the same difficulty as in the case of the iron compounds (see Lect. XXV.): the greater part of the lime is excreted through the intestines, only a small proportion finding its way into the urine. On this point compare Fr. Voit, *Zeitschr. f. Biolog.*, vol. xxix. p. 325: 1893. Here also will be found an account of the earlier work on the subject. Compare also Rüdel, *Arch. f. exper. Path. u. Pharm.*, vol. xxxiii., pp. 80 and 90, 1893.

[3] H. Stilling and J. v. Mering, *Centralbl. f. d. med. Wissensch.*, p. 803: 1889; L. Gelpke, "Die Osteomalacie im Ergolzthale": Basel, 1891.

human milk. This may be teleologically explained by the fact that the calf grows much more rapidly than the infant. It is therefore probable that the adult organism could exist with a very small amount of salts; in fact, it is *à priori* difficult to see what the constant addition of salts is required for. Inorganic salts serve a totally different purpose to the organic food-stuffs. The latter act as sources of energy; chemical potential energy is introduced with them into our tissues, and is converted by the decomposition and oxidation of these organic substances into all those forms of kinetic energy which make up life as understood by our senses. They serve us by the very fact of their decomposition. The necessity for their constant renewal is not only a matter of experience; it is also at once apparent on *à priori* grounds. Inorganic salts must be regarded from a different point of view. These are already saturated compounds of oxygen, or chlorids, which likewise have no affinity for oxygen. No energy is set free in the body by their decomposition and oxidation; they can in no way become used up and useless. Why therefore are they renewed? Even water behaves differently to the salts; it assists in the elimination of the waste products of metabolism. The kidneys can only separate the nitrogenous substances when in a watery solution. The diffusion of gases in the lungs is only possible while the surface of the lungs is moist. The expired air is saturated with watery vapor. The evaporation of water from the surface of the skin plays a most important part in regulating the heat of the body. The *à priori* necessity for a constant supply of water is thus likewise evident. But it is otherwise with the salts. It is conceivable that if only the organic aliments and water always entered the organism in sufficient quantity, the inorganic salts arising from the decay of the tissues might again be used in the reconstruction of the tissues. Even if a little waste were unavoidable, as by excretion with the feces in consequence of incomplete absorption of the gastric juices, by the scaling off of the epidermis, the loss of hair, &c., yet we might expect that the full-grown organism would cling firmly to its store of salts, and would require but a very small additional supply. The constant supply of salts in considerable quantities is not an *à priori* necessity for the adult.

We must therefore determine the question by experiment. We might feed a full-grown animal for a long period exclusively on organic food-stuffs and water, and ascertain the disturbances that would occur, and the length of time it would live on such a diet. This fundamental experiment in metabolism had, until quite recently, only once been made by Forster, Voit's assistant in Munich.[1]

Forster met with insuperable difficulties when he tried to obtain food free from ash. It is possible to get carbohydrates and fats free from ash, but no one has yet succeeded in separating proteid from all inorganic matter. Even crystalline proteid contains all the constituents of ash in small quantity. Forster, in his experiments, employed the residue of the meat left from the preparation of Liebig's extract of meat. After boiling it repeatedly with distilled water and drying, it still contained 0.8 per cent. of ash. Forster fed two dogs on this proteid containing this small amount of salts, as well as on fat, sugar, and starch-flour. He also fed three pigeons on starch-flour and casein, which likewise contained very little saline ingredient.

Forster observed that the animals died remarkably quickly when fed on this diet. The three pigeons lived thirteen, twenty-five, and twenty-nine days. One of the dogs was "so ill at the end of thirty-six days that he would certainly have died in a short time if the experiment had been continued, while the other was dying at the end of twenty-six days." When completely deprived of food, dogs live from forty to sixty days. Food from which the organic salts have been removed appears to be more rapidly fatal than the deprivation of all food.

Forster concludes, from these experiments, that the full-grown animal requires considerable quantities of inorganic salts. An objection may however be raised to this conclusion, for there is one condition to which Forster has omitted to draw attention—I mean the formation of free sulphuric acid from the sulphur of the proteid.

Proteid contains from $\frac{1}{2}$ to $1\frac{1}{2}$ per cent. of sulphur which, in the decomposition and oxidation of proteid, is converted into sulphuric acid. Eighty per cent. of the sulphur taken in food appears in this form in the urine. Under normal conditions this sulphuric acid is united with the bases which are taken up with every form of animal and vegetable food. Animal food contains basic phosphates of the alkalies, carbonates of the alkalies, and alkali-albuminates; vegetable food yields in addition the alkaline salts of vegetable acids, such as tartaric, citric, malic, &c., which in the organism are converted into carbonates by oxidation. These bases saturate the sulphuric acid formed from proteid. If the basic salts are removed from the food, this powerful acid finds no bases at hand to neutralize

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[1] J. Forster, *Zeitschr. f. Biolog.*, vol. ix. p. 297: 1873.

it, and consequently attacks those bases which are integral constituents of the living tissues; figuratively, it may be said to wrench individual bricks out of their places, and thus to induce the destruction of the edifice.[1] This appears to me to be the cause of the rapid death in the animals experimented upon by Forster. The remarkable fact that the dogs died in a shorter time than when simply starved, would be explicable on this ground.[2] The correctness of this reasoning has been tested experimentally by Lunin.[3]

Lunin fed a certain number of his animals with food deprived of its mineral constituents; the others were treated in a similar way, but with an addition of carbonate of soda which was just sufficient to neutralize the sulphuric acid formed from the sulphur of the proteid.

It was important to use as large a number of animals as possible, in order to eliminate the influence of accidental factors and thus arrive at a reliable result. Mice were therefore chosen for the purpose, since it would have been almost impossible to obtain food free from mineral constituents in the quantity requisite for a number of large animals.

The food was prepared in the following manner. By precipitating diluted milk with acetic acid, and washing the finely flocculent coagulum with water acidified with acetic acid, a mixture of fat and casein was obtained, which only contained from .05 to .08 of ash in 100 parts of dry matter, therefore ten times less salts than in the experiments of Forster. To this mixture, cane sugar deprived of its ash was added as a representative of the third group of food-stuffs.

On this food and distilled water, five mice lived eleven, thirteen, fourteen, fifteen, and twenty-one days. Two mice that were completely starved, lived four days: two more only three days.

Again, six mice were fed upon the same food with the addition of carbonate of soda. These lived sixteen, twenty-three, twenty-four, twenty-six, twenty-seven, and thirty days, therefore twice as long as the animals which had no base to saturate the sulphuric acid formed.

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[1] As we shall see later on (*vide* Lecture XIX.), the organism of the dog is able to protect itself against the injurious action of free acids, by splitting off ammonia from the nitrogenous organic compounds. But this power is not unlimited, and it is doubtful whether the ammonia is invariably present in the particular cells in which the sulphuric acid thus liberated begins its work of destruction.

[2] G. Bunge, *Zeitschr. f. Biolog.*, vol. x. p. 130: 1874.

[3] N. Lunin (Bunge's laboratory), "Ueber die Bedeutung der anorganischen Salze für die Ernährung des Thieres," Dissert.: Dorpat, 1880. Reprinted in *Zeitschr. f. physiol. Chem.*, vol. v. p. 31: 1881.

It might be objected that the animals lived longer, not because of the neutralization of the sulphuric acid, but because they obtained at least one inorganic ingredient. This objection is answered by the following experiment, in which seven mice were given, *ceteris paribus*, instead of the carbonate of soda, an equivalent quantity of chlorid of sodium—that is, a neutral salt incapable of neutralizing the sulphuric acid. The seven mice expired after six, ten, eleven, fifteen, sixteen, seventeen, and twenty days. In this case, although they received two inorganic substances, sodium and chlorin, they lived only half as long as the animals which received but one, sodium, and in fact no longer than the animals which had no inorganic addition at all. The experiments were in complete accordance with my deductions. As a control, two parallel series of experiments with potassium chlorid and potassium carbonate were carried out, and gave precisely the same results.

By preventing the formation of free sulphuric acid, the animals lived twice as long, but still for a very short period. As the action of the acid could not have caused their death, what made the mice die? Was the composition of the organic food-stuffs insufficient? In order to decide this question, all the inorganic salts of milk were added to the same artificial mixture of organic food, in the exact proportions in which they exist in the ash of milk, and in the same relation to the amount of organic matter as in milk. Six mice lived twenty, twenty-three, twenty-three, twenty-nine, thirty, and thirty-one days upon this mixture—no longer than they did with the carbonate of soda only. Of three mice which were fed exclusively on cow's milk, one died after forty-seven days, and, as dissection showed, of intussusception (compare p. 72); the two others lived in their cage for two and a half months, grew considerably fatter, and were in capital condition when the experiment ceased.

It is a noteworthy fact that, although animals can live on milk alone, yet if all the constituents of milk which according to the present teaching of physiology are necessary for the maintenance of the organism be mixed together, the animals rapidly die. Cannot cane sugar take the place of sugar of milk? Or are the inorganic and organic constituents of milk chemically combined, and only assimilable in this combination? On precipitation of the casein by acetic acid, the small amount of proteid in the milk remained in solution. Cannot this proteid be replaced by the casein? Or does milk contain, in addition to proteid, fat, and carbohydrates, other organic substances, which are also indispensable to the maintenance of life? It would be worth while to continue the experiments.

The question as to the need of adult animals for inorganic salts cannot be considered as settled. Before it can be decided, we must become intimately acquainted with all the organic food-stuffs which are indispensable; we must also manage to combine them in such a way that they may be palatable to the animals during lengthened experiments. Finally, we must be able to saturate the sulphuric acid resulting from the proteid—by means of a harmless organic base, such as cholin—without the addition of inorganic bases. But even then it would probably be impossible to come to a decision, because it is beyond our power to ensure the presence of the base at the spot where the sulphuric acid is set free, or because the sulphates, formed with the base thus artificially introduced, expel the normal salts from the tissues. The difficulty appears for the present to be insuperable.

There is only one inorganic salt about which I must add a few words, because it holds a rather exceptional position—common salt.

It is a very remarkable fact that of all the inorganic salts in our bodies we only take one with our organic food-stuffs, and that is common salt. We obtain enough of all the other salts from the amount contained in our food, and we never think of providing ourselves with them separately. Common salt forms the only exception, which is the more remarkable as our diet is by no means deficient in it. All vegetable and animal food contains considerable quantities of chlorin and sodium. Why do these quantities not suffice, and why do we add common salt?

In the earlier experiments made to decide this point, one fact was quite overlooked, which appears to me likely to lead to a correct solution of the difficulty. I mean the fact that the desire for salt in the food was only observed in the case of herbivora, and never in the case of carnivora. Our carnivorous domestic animals, the dog and the cat, prefer unsalted to salted food, and show great dislike to very salt food, while the domesticated herbivora are well known to be very fond of salt. The same thing has been observed in wild animals. It is a known fact that wild ruminants and hoofed animals seek out salt-rocks and pools, and places where salt effloresces, to lick the salt, and that hunters watch for them at such places, or expose salt as a bait. This has been noticed by numerous travellers to hold good for herbivora of all countries and climates, but it has never been observed in the case of beasts of prey.

The difference is the more striking as the amount of salt which herbivorous animals take in with their food is, compared with the weight of the body, generally not much less than that consumed by carnivorous animals. On the other hand there is a considerable difference in another constituent of the ash of their food, in the potassium. Herbivorous animals take at least three or four times as much of salts of potassium as the carnivora. This fact leads me to imagine that the abundance of potassium in vegetable food is the cause of the need for salt in the herbivora.

If, for instance, a salt of potassium, such as potassium carbonate, meets with common salt or chlorid of sodium in solution, a partial exchange takes place; chlorid of potassium and carbonate of sodium are formed. Now chlorid of sodium is well known to be the chief constituent among the inorganic salts of blood-plasma. When, therefore, salts of potassium reach the blood by the absorption of food, an exchange takes place. Chlorid of potassium and the sodium salt of the acid which was combined with the potassium are formed. Instead of the chlorid of sodium, therefore, the blood now contains another sodium salt, which did not form part of the normal composition of the blood, or at any rate not in so large a proportion. A foreign constituent or an excess of a normal constituent, *i. e.*, sodium carbonate, has arisen in the blood. But the kidneys possess the function of maintaining the same composition of the blood, and of thus eliminating every abnormal constituent and any excess of a normal constituent. The sodium salt formed is therefore ejected by the kidneys, together with the chlorid of potassium, and the blood becomes poorer in chlorin and sodium. Common salt is therefore withdrawn from the organism by the ingestion of potassium salts. This loss can only be made up from without, and this explains the fact that animals, which live on a diet rich in potassium, have a longing for salt.

I have proved the correctness of this deduction by experiment. To a diet of uniform character salts of potassium were one day added, the consequence being a striking increase in the excretion of chlorin and sodium. I have tried this experiment on myself with all the salts of potassium which are concerned in human nutrition. Eighteen grammes K_2O, as phosphate or citrate, divided into three doses during the day, caused a loss to the body of 6 grms. of common salt, besides 2 grms. of sodium; for the potassium salts effect an exchange, not only with the chlorid, but also with other compounds of sodium, as albuminate, carbonate, and phosphate.

The amount of potassium taken in these experiments was not large—in fact, much less than that introduced with the most important vegetable articles of diet; and yet 6 grms. of salt were withdrawn from the organism by it. This is about one-half of the common salt which is contained in the 5 liters of a man's blood. That other tissues likewise suffer by this loss is undoubted. But in the first instance the blood is chiefly affected, and I think that if this loss in the blood was covered by a comparatively small loss in the other tissues, a fresh addition of potassium must have the effect of producing a fresh loss of sodium. Experiments of this kind have not so far been made. It has not yet been ascertained up to what point the body will continue to give up sodium, when potassium is constantly taken. There is no doubt that a point would soon be reached at which the body would stoutly retain its remaining sodium.

But even those quantities of chlorin and sodium, the loss of which I have specially investigated, appear to me sufficiently large to account for the need to replace them caused by eating vegetables containing an abundance of potassium. Having regard to the important part which salt plays in the organism (as in the formation of the digestive secretion, or in dissolving the globulins), even a small diminution may be prejudicial to certain functions, and may give rise to the need of recovering the loss.

As already mentioned, the amount of potassium taken in my experiments was not more than 18 grms. A man who lives chiefly on potatoes takes, in the course of the day, up to 40 grms. of potassium. This shows why potatoes are so unpalatable without salt, and are eaten everywhere with well-salted adjuncts. Like potatoes, all the other important vegetable articles of diet, the cereals and leguminosæ, are very rich in potassium, and this explains the fact that country people, living mainly on a vegetable diet, use more salt than the inhabitants of towns, who eat a great deal of animal food. It has been statistically shown in France that people living in the country eat three times as much salt per head as those in towns.

We may now ask what the people do who take no vegetable food at all. There are whole tribes of hunters, fishermen, and other nomads, who live entirely on animal food. We might expect that these people would, like the carnivorous animals, have a disinclination for salt. This is in fact the case. In order to ascertain this, I have gone through a very large number of works of travel, and have obtained a great deal of information from recent travellers, either personally or by letter. From all this it appears to be a universal rule that in all times and in all lands those people who live entirely upon animal food either have never heard of salt, or, if they possess it, avoid it; whereas the people whose staple food is vegetable have the greatest desire for it, and regard it as an indispensable article of diet.

This difference was manifested as far back as the ancient Greek and Roman times, when the sacrificial animals were always offered to the gods without salt, but the fruits of the earth with salt. The Mosaic law expressly commanded the Jews to present their vegetable offerings accompanied by salt to their Deity.[1]

The Indo-Germanic languages have no common word for salt, just as they have none for farming industries, whereas the terms used in cattle-breeding may mostly be traced back to common roots. This probably shows that the Indo-Germanic tribes knew nothing about salt so long as they were wandering about—an undifferentiated nation—pasturing their flocks on the summit and slopes of the mighty Bulur-Tagh. They first became acquainted with it after their dispersion, when they began farming and took to vegetable food. In the time depicted by Tacitus, we find the Germans just adopting fixed places of abode, and beginning to devote themselves to agriculture. But at this time they did not know how to obtain a regular supply of salt, although the desire for it was already awakened in them, since Tacitus gives accounts of raging and decimating wars, which were carried on by different tribes for the possession of the salt-mines on the frontiers.

The Finnish languages have up to the present day no word for salt. The western Finlanders, who are now engaged in farming, use salt and call it by the German name. On the other hand the eastern Finlanders, who still lead hunters' and nomads' lives, use no salt whatever, and this is the case with all the other hunting, fishing, and nomadic tribes in the north of Russia and in Siberia. It is not because they are unacquainted with salt, or cannot procure it, but because they have a decided dislike to it. In all parts of Siberia there are rock-salt strata, salt lakes, and salt efflorescences. The Siberian hunters are only interested in these salt strata because the flocks of reindeer assemble in these places to lick the salt; the hunters themselves devour their meat without it. A large number of Siberian travellers have informed me, both personally and by letter, that such is the case with all the Siberian tribes. The mineralogist, C. von Ditmar, who

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[1] The sources of these and all following statements concerning the use of salt among different nations are quoted in my work, "Ethnologischer Nachtrag zur Abhandlung über die Bedeutung des Kochsalzes, u. s. w.," *Zeitschr. f. Biolog.*, vol. x. p. 111: 1874.

travelled over the whole of Siberia between 1851 and 1856, and lived for a long time among the Kamtschadales, writes to me as follows: "I have frequently in my travels, given those people (Kamtschadales, Korachs, Tschuktsches, Ainos, Tunguses) some of my salted viands to taste, and have noticed the grimaces they made, showing how much they disliked it." Ditmar relates how the Kamtschadales live chiefly on fish, which they throw into large holes dug in the ground, where the whole mass is soon turned into a "stinking jelly." The Russian Government, disapproving of the Kamtschadales' favorite food, which is certainly disgusting to any European and must be unwholesome, endeavored to introduce the salting of fish by stringent regulations. Arrangements were made at Petropaulowski for obtaining salt from sea-water, and the salt was sold to the Kamtschadales at a nominal price. The Kamtschadales, who are an uncommonly docile race, obeyed orders, and the fish was conscientiously salted. But they did not eat it. They kept to their decomposing fish; and at the time that Ditmar was in Kamschatka, the Russian Government had relinquished the task of persuading them as hopeless. Only the old people still spoke of that period as of a time of plague. Ditmar relates that the descendants of the Russians in Kamschatka do cultivate European vegetables, but only in small quantities, that they prefer the Kamtschadales' bill of fare, and accordingly their use of salt has gradually diminished. Vegetables and cereals are only eaten in any quantity in Petropaulowski, and here, on the other hand, the salt-cellar is always on the table.

The astronomer, L. Schwarz, informed me that on his travels in the country of the Tunguses, he lived exclusively on reindeer-flesh and game. This diet agreed perfectly with him, and he never experienced any wish for salt.

But as it might be thought that the disinclination of the Siberian tribes for salt might be due, not to the animal food, but to the northern climate, I will refer to the accounts of the inhabitants of warm countries who live on an animal diet, and yet take no salt.

In the Neilgherry Hills in India, a pastoral tribe, the Tudas, was first discovered during the present century. Owing to their being surrounded by fever marshes, the English had always been prevented reaching them. They were totally unacquainted with vegetable food, and lived on milk and buffalo-meat, knowing nothing of salt.

The Kirghese also live on meat and milk, and never use salt, although they are inhabitants of the salt steppes. I was informed of this by Baron Maydell, who travelled through the Kirghese Steppes in 1845 and in 1847.

Sallust relates the same thing of the Numidians: "Numidæ plerumque lacte et ferina carne vescebantur et neque salem neque alia irritamenta gulæ quærebant." There is an abundance of salt on the north coast of Africa.

At present there are certain tribes of Bedouins in Arabia who live under conditions similar to those of the Numidians in the time of Sallust. In Wrede's Travels it is stated that the Bedouins eat meat without salt, and appear to consider the use of salt as altogether ridiculous.

The Bushmen in the south of Africa live by the chase, and do not use any salt.

The negro races on the contrary are agriculturists. The interior of Africa contains but little salt. At the present time the negroes are plentifully supplied with salt, both by importation and by salt-boiling on the coast. Among the older travellers, Mungo Park gives the following description of the longing of the negroes for salt: "In the districts of the interior, salt is the greatest of all delicacies. It strikes a European very strangely to observe a child sucking a piece of rock-salt as if it were sugar. I have frequently seen this done, although the poorer class of inhabitants in the interior are so badly provided with this costly article, that to say that a man eats salt with his meal is equivalent to saying that he is rich. I myself have found the scarcity of this natural product very trying. Constant vegetable food causes a painful longing for salt that is quite indescribable. On the coast of Sierra Leone the desire for salt was so keen among the negroes that they gave away wives, children, and everything that was dear to them, in return for it."

The Indians of North America are well known to have been hunters and fishermen at the time of their discovery; they did not use salt, although the North American prairies are full of it. Only a few tribes on the lower course of the Mississippi were diligent tillers of the soil at the time of the first invasion of the Spaniards. It is related of these tribes that they waged wars about the salt-springs.

The Mexicans were farmers, and understood the methods of obtaining salt. The same account is given of the natives whom Columbus met with in the West Indian Islands.

The shepherds of the South American pampas, who live entirely on meat and regard vegetable food as fit only for animals, do not use any salt, although the pampas abound in numberless salt-lakes and incrustations. The neighboring

Araucanians, on the other hand, who were farmers at the time of the discovery of America, made use both of sea-salt and rock-salt. The inhabitants of New Holland were hunters, and employed no salt.

Most of the tribes of Australia and of the East Indian Archipelago live on a mixed diet, and get enough salt from the marine animals that they eat. But there is an account of one purely agricultural tribe in the tropical islands, where the people live almost exclusively on the produce of the field, which is rich in potassium. They are the Battas in Sumatra. We should expect that these people would have a great desire for salt. For a long time I was unable to find any account about it in any books of travel, till at last I lighted upon a passage in a chapter describing their modes of legal procedure, in which it said that the solemn form of oath in use among them ran as follows: "May my harvest fail, my cattle die, and may I never taste salt again, if I do not speak the truth."

From the above facts we see that at every period, in every part of the world, and in every climate, there are people who use salt as well as those who do not. The people who take salt, though differing from each other in every other respect, are all characterized by a vegetable diet; in the same way, those who do not use any salt are all alike in taking animal food. We see that whole tribes, when forsaking their nomadic life for an agricultural one, begin the use of salt; and that, *vice versâ*, people who have been accustomed to take salt, cease to do so when they emigrate and settle down among a flesh-eating population. We see that European travellers, if their supply of salt fails them in foreign countries, do not feel any want of it if they are living on animal food; but that, on the other hand, they experience "a painful longing" for it if they adopt a vegetarian mode of diet. The causal connection between vegetable food and the need for salt is undeniable. It might be still doubted whether it is really the abundance of potassium in the vegetables which causes this need. The occurrence of potassium in considerable quantity is not the only difference between vegetable and animal food. The following facts may serve to confirm my view of the matter:—

One important article of vegetable diet, rice, is very poor in potassium salts. Rice contains six times less potassium than the European cereals (wheat, rye, barley), from ten to twenty times less than the leguminosæ, and from twenty to thirty times less than the potato. If we consume enough rice to yield 100 grms. of proteid, we only take in 1 grm. K_2O from the same source. But if we consume 100 grms. of proteid in the form of potatoes, we should at the same time obtain above 40 grms. K_2O. We should therefore expect people who only take rice and no other vegetable with their meat to have no desire for salt. This is in fact the case, and is universally recorded of certain tribes of Bedouins on the Arabian Peninsula, and of a few races in the East Indian Islands.

L. Lapicque has objected to my hypothesis on the grounds that certain negro races, who can obtain no common salt, use instead as an adjunct to their vegetable food the ashes of a plant consisting chiefly of potassium salts. I cannot regard my hypothesis as controverted by this fact, unless it were shown that these negroes had a choice between common salt and salts of potash and gave the preference to the latter. If however they are driven by need to the potash salts, it is possible that we have here merely an example of disordered instinct, for which we have other analogies. A man who has always taken alcohol instead of water to quench his thirst prefers the former to the latter, although the alcohol has the effect of increasing rather than of diminishing his thirst.

The amount of potassium and sodium in the different articles of vegetable and animal food eaten by man and animals may be gathered from the following tables :

TABLE I.

IN 1000 PARTS OF DRIED SUBSTANCES THE PROPORTIONS ARE—

Arranged according to increasing amount of potassium.			Arranged according to increasing amount of sodium.	
	K_2O.	Na_2O.		Na_2O.
Rice	1	0.03	Rice	0.03
Bullock's blood	2	19.0	Apples	0.07
Oats	5–6	0.1– 0.4	Beans	0.13
Wheat			Peas	0.17
Rye			Clover	0.17
Barley			Oats	0.1– 0.4
Dog's milk	5–6	2.0– 3.0	Wheat	
Human milk	5–6	1.0– 2.0	Barley	
Apples	11	0.1	Rye	
Peas	12	0.2	Potatoes	0.3–
Milk of herbivora	9–17	1.0–10.0	Hay	0.3– 1.5
Hay	6–18	0.3– 1.5	Human milk	1.0– 2.0
Beef	19	3.0	Dog's milk	2.0– 3.0
Beans	21	0.1	Milk of herbivora	1.0–10.0
Strawberries	22	0.2	Beef	3.0
Clover	23	0.1	Bullock's blood	19.0
Potatoes	20–28	0.3– 0.6		

We see from the second table that the beast of prey, which devours every part of an animal, obtains potassium and sodium in almost equal quantity. This is the case, not only with mammals, but with the whole class of vertebrates.[1] On the other hand, four equivalents of potassium are present for every equivalent of sodium in the bloodless meat of slaughtered animals. It is therefore noteworthy that the people who live on an animal diet without salt, carefully avoid loss of blood when they slaughter the animals. This was told me by four different naturalists, who have lived among flesh-eaters in various parts of northern Russia and Siberia. The Samoyedes, when dining off reindeer-flesh, dip every mouthful in blood before eating it. The Esquimaux, in Greenland, are said to plug the wound as soon as they have killed a seal.[2] Among the Masai, a tribe of eastern equatorial Africa, who during their period as warriors from seventeen to twenty-four years of age, live exclusively on an animal diet without salt, blood is regarded as the choicest and most desirable of all articles of food.[3]

TABLE II.

FOR ONE EQUIVALENT Na_2O THE EQUIVALENTS OF K_2O ARE

	Equivalent K_2O		Equivalent K_2O
Bullock's blood	0.07	Barley	14–21
Egg-albumin	0.7	Oats	15–21
Yolk of egg	1.0	Rice	24
The whole body of mammals	0.7– 1.3	Rye	9–57
		Hay	3–57
Milk of carnivora	0.8– 1.6	Potatoes	31–42
Mangel-wurzel	2.0	Peas	44–50
Human milk	1.0– 4.0	Strawberries	71
Milk of herbivora	0.8– 6.0	Clover	90
Beef	4.0	Apples	100
Wheat	12.0–23.0	Beans	110

The two bases are also contained in the milk of carnivora in equal proportions, whereas potassium generally preponderates largely in the milk of herbivora and in human milk, as

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[1] A. von Bezold, "Das chemische Skelett der Wirbelthiere," *Zeitschr. für wissenschaftl. Zoologie*, vol. ix. p. 241: 1858; G. Bunge, *Zeitschr. f. Biolog.*, vol. x. p. 318: 1874.

[2] The exact source of these facts is given in the *Zeitschr. f. Biolog.*, vol. x. p. 115 (note): 1874.

[3] *Vide* H. H. Johnston, "Kilimandjaro."

may be seen by a reference to Table II. This shows that man and herbivora can do very well on a diet, in which the relation is from four to six equivalents of potassium to one equivalent of sodium, without any addition of salt. And there are many vegetables in which the proportion is no higher. In hay, which is a mixture of all kinds of herbage, the proportion is sometimes, as the above table shows, only as three to one. It is a fact that many wild herbivorous mammals, such as hares and rabbits, never eat salt, and in many places it is not offered to herbivorous domestic mammals. A keen desire for salt would only be awakened in these animals if they were exclusively fed on one of the varieties of herbage containing both the most potassium and the least sodium, such as clover. The wild herbivora perhaps instinctively avoid browsing only on the herbage that contains the largest proportion of potassium. But the domesticated animals would suffer if they were given food that was very rich in potassium, without salt. I will not affirm that they could not exist under this treatment, although farmers have found by experience that the animals eat more and thrive better if they are allowed to have salt, and even that obvious ill-effects follow a complete abstinence from this article.[1] Nor do I maintain that human beings cannot exist without salt on a diet almost entirely vegetarian. But if we had no salt, we should have a strong disinclination to eat large quantities of a vegetable rich in potassium, such as potatoes. The use of salt enables us to employ a larger variety of the earth's products as food than we could without it.

It is particularly worthy of note that those articles of diet in which, according to Table II., the proportion of potassium to sodium is the highest, such as rye, potatoes, peas, and beans, are the very ones that form the staple food of the lower classes in Europe. The injustice of a salt-tax is therefore apparent, for the poorer a man is the more he is forced to live on the vegetables containing the largest amount of potassium, and the greater his consumption of salt in consequence.

In passing, I must call attention to the fact that we are accustomed to take far too much salt with our viands. Salt is not only an aliment, it is also a condiment, and easily lends itself, as all such things do, to abuse. A glance at Table III. shows us how little salt need be added to most articles of diet

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[1] Barral, "Statique chimique des animaux, appliquée spécialement à la question de l'emploi agricole du sel": Paris, 1850; Boussingault, *Ann. de Chim. et de Phys.*, sér. 111, vol. xxii. p. 116: 1848. Demesmay, *Journal des Économistes*, vol. xxv. pp. 7, 251: 1849; Desaive, "Ueber den vielseitigen Nutzen des Salzes in der Landwirthschaft," Deutsch von Protz: Leipzig, 1852.

in order to preserve the same proportion of the alkalies as in milk. For instance, from 1 to 2 grms. of salt in the day would be sufficient to add to a diet of cereals and leguminosæ, or a few decigrammes to a diet of rice. Instead of this, most people take from 20 to 30 grms. daily, and frequently even more.

TABLE III.

FOR EVERY ONE HUNDRED GRMS. OF PROTEID WE GET—

	K_2O.	Na_2O.
Bullock's blood	0.2 grms.	2.0 grms.
Rice	1.0 "	0.03 "
Beef	2.0 "	0.3 "
Wheat Rye Peas	2.0–5.0 "	0.05–0.3 "
Human milk	5.0–6.0 "	1.0 –2.4 "
Potatoes	42 "	0.7 "

We must ask whether our kidneys are really able to eleminate such large quantities of salt? Do we not impose too great a task upon them, and may it not be fraught with serious consequences? When on a diet of meat and bread, without salt, we excrete not more than from 6 to 8 grms. of alkaline salts in twenty-four hours. With a diet of potatoes, and a corresponding addition of salt, over 100 grms. of alkaline salts pass through the kidneys in the day. May not there be danger in this? The habit of drinking spirituous liquors, which moreover is reckoned one of the causes of chronic nephritis, also brings about the immoderate use of salt,[1] and thus one sin against nature leads to another. These are questions to which I would direct the attention of practitioners.

There is no organ in our body so mercilessly ill treated as the kidneys. The stomach reacts against overloading. The kidneys are obliged to let everything pass through them, and the harm done to them is not felt till it is too late to avoid the evil consequences.

I would further call attention to the slight amount of work that devolves upon the kidneys when rice is the staple food. Only 2 grms. of alkaline salts are excreted in twenty-

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[1] Compare H. Keller (Bunge's laboratory), *Zeitschr. f. physiol. Chem.*, vol. xiii. pp. 130 and 134: 1889.

four hours. The superiority of rice (which has for centuries been the food of the majority of mankind—Persians, Indians, Chinese, Japanese) over potato is evident. Should not rice be employed as a chief article of diet in patients with renal disease? The same with affections of the stomach, for the potassium salts act as a powerful irritant to the gastric mucous membrane,[1] and rice contains less of these than any other article of food.

I cannot leave this subject without, in conclusion, giving expression to one other theory which is becoming more and more a conviction with me, and in proof of which I have carried out a series of troublesome experiments. I have not hitherto ventured to publish them, because I was well aware that the theory might be thought very fanciful while the grounds upon which it was built were still so scanty. I am however convinced that the remarkably high percentage of salt in vertebrate animals, as well as the desire to take salt with our food, can only be satisfactorily explained by the theory of evolution.

Let us glance at the distribution of the two alkalies, potassium and sodium, over the whole surface of the globe. In our introductory remarks on the circulation of the elements, I mentioned the struggle that went on between the carbonic acid and the silicic acid for the possession of the bases (see p. 15). In this conflict the carbonic acid shows a greater affinity for sodium, and the silicic acid for potassium. By the action of the weather on silicic rocks, the sodium, after decomposition, is dissolved in water as a carbonate, and trickles with the water into the ground. The potassium on the contrary, with other bases, especially alumina, remains combined with the silicic acid, and continues to lie on the surface as an insoluble double salt. When the sodium carbonate reaches the sea by means of springs, streams, and rivers, it is converted by the chlorids of the alkaline earths into common salt, the insoluble carbonates of the alkaline earths are formed, which sink to the bottom, and are continually building up whole mountain ranges in the shape of lime, chalk, and dolomite. Sea-water is thus rich in common salt, poor in potassium salts, while the surface of dry land is rich in potassium salts and poor in common salt.

The amount of common salt in the organism corresponds with the amount in the environment. Sodium differs in this respect from potassium, which is an integral, indispensable

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[1] G. Bunge, *Zeitschr. f. Biolog.*, vol. ix. p. 130: 1873; and Pflüger's *Arch.*, vol. iv. pp. 277, 280: 1871.

constituent of every vegetable and animal cell. Every cell has the power of withdrawing and of assimilating the requisite amount of this base, even from the most scantily supplied soil. All sea and land plants therefore contain an abundance of potassium. Sodium on the other hand does not appear to play such an important part. Many plants contain only traces of sodium; those which are rich in it are only the sea-weeds and the plants which grow on the sea-shore, and on the salt steppes which are dried-up sea-basins. There are only a few apparent exceptions to this rule, as for instance in the classes of Chenopodium and Atriplex. But these species thrive only in a saline soil; they are closely allied to the denizens of the salt steppes, and have probably migrated from there. Among cultivated plants, the *Beta altissima*, which also belongs to the Chenopodiaceæ, is the only one rich in sodium, and this was originally indigenous on the sea-coast.

This is also the case with invertebrate animals; only those which live in the sea, and those nearest allied to them on land, contain much salt. The typical representatives of land invertebrates, the insects, have very little salt in them. I have myself made an analysis which proves that they do not contain more sodium than the plants from which they derive their nourishment.

The land vertebrates are all remarkably rich in salt, in spite of the scanty supply around them. But even these are only apparent exceptions. We need but remember the fact that the first vertebrates on our planet all lived in the sea. Is not the large amount of chlorid of sodium found in the present inhabitants of dry land another proof of the genealogical connection which we are forced to accept from morphological facts? There is no doubt that each of us in his individual development has gone through a stage in which he still possessed the chorda dorsalis and the branchial arches of his sea-dwelling ancestors. Why may not the high average of salt in our tissues be also inherited from them?

If this interpretation be correct, we should expect that the younger the vertebrates are in their individual development, the more salt they would possess. This is in fact the case. I have convinced myself by numerous experiments that an embryo of a mammal contains more salt than a new-born animal, and that it gradually becomes, after birth, poorer in chlorin and sodium as it develops. Cartilage contains the most sodium of any tissue in our bodies, besides being also the tissue of greatest antiquity. It is histologically identical with the tissue which still survives in the skeleton of the

Selachians, a salt-water animal, during its whole life. The human skeleton, as every one knows, is originally also composed of cartilage, and even before birth much of this is replaced by bone. This phenomenon cannot be understood on teleological grounds; it can only be explained by the theory of evolution. We cannot assume that the cartilage period must be passed through in order that the bone may develop from the cartilage. This is not the fact. Bone does not arise from cartilage. The cartilage is entirely absorbed, and the bone grows from the perichondrium to take the place of the cartilage. And moreover the oldest formation, the cartilage, also contains the largest proportion of sodium.

These are facts which lead most readily to the interpretation that the vertebrates living on dry land originally came from the sea, and are still continuing to adapt themselves to their present surroundings, where they can get but little salt. We prolong this process of acclimatization by taking advantage of the salt strata which have been left on the land by our primeval element, the salt flood.

LECTURE VIII

MILK AND THE FOOD OF INFANTS

We have already had occasion in considering food-stuffs to make frequent mention of milk, the nourishment which nature provides for the growing organism, and we may now consider this subject more in detail.

In the following table I give the results of the analyses of milk,[1] so far as they have been carried out up to the present time:—

One Hundred Parts of Milk Contain—

	Human.			Dog.	Cat.	Rabbit.	Guinea-pig.	Sow.	Elephant.
	I.	II.	III.						
Casein	—	1.2	—	5.2	3.1	—	—	—	—
Albumin	—	0.5	—	1.9	6.4	—	—	—	—
Total proteids	1.7	1.7	1.5	7.1	9.5	15.5	11.2	5.9	3.1
Fat	3.1	3.8	3.3	12.5	3.3	10.5	45.8	6.9	19.6
Sugar of milk	5.9	6.0	6.5	3.5	4.9	2.0	1.3	3.8	8.8
Ash	0.2	0.2	0.3	1.3	0.6	2.6	0.6	1.1	0.7

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[1] In the cases of mare's, cow's, goat's, and sheep's milk, I have taken the average figures as calculated by J. König in his "Chemistry of Human Food-stuffs," 3d edition, Berlin, 1889. The few older and less reliable analyses have been superseded by the numerous later ones carried out according to accurate methods. For sow's milk I have, in calculating the average composition, adopted only the last four of König's nine analyses since the earlier analyses, in consequence of the incomplete extraction of the casein precipitate with ether, obviously give too small an amount of fat and too large a one of casein. For the same reason I have only employed for dog's milk two analyses of my pupil Fr. Pröscher, in which the fat was completely extracted by means of the Soxhlet apparatus (*Zeitschr. f. physiol. Chem.*, vol. xxiv. p. 290: 1897). The analysis of rabbit's milk is by A. Pizzi (*Le staz. sperim. agric. ital.*, vol. xxvi. p. 615: 1894); that of reindeer milk by Fr. Werenskiold (*Chemikerzeitung*, vol. xix., 1895); that of porpoise milk by Frankland (*The Chemical News*, vol. lxi. p. 63: 1890). The mean figures for the milk of the remaining animals are reckoned from the small number of analyses which have so far been made and are to be found in König's work. Finally, as regards human milk, nearly all the analyses have been carried out by inaccurate methods. After close investigation, it seems to me that the analyses of the following authors are the most worthy of confidence: (1) Emil Pfeiffer, *Jahrb. f. Kinderheilkunde*, vol. xx. p. 389: 1883; (2) Julius Lehmann, Pflüger's *Arch.*, vol. lvi. p. 577: 1894; (3) Söldner, *Zeitschr. f. Biolog.*, vol. xxxiii. p. 66: 1896. The average compositions obtained by these three authors are given separately in the following tables as

One Hundred Parts of Milk Contain (*continued*)—

	Horse.	Donkey.	Cow.	Goat.	Sheep.	Reindeer.	Camel.	Llama.	Porpoise. (*Globiocephalus melas.*)
Casein	1.2	0.7	3.0	3.2	5.0	8.4	—	3.0	—
Albumin . . .	0.8	1.6	0.5	1.1	1.6	2.0	—	0.9	—
Total proteids .	2.0	2.2	3.5	4.3	6.5	10.4	4.0	3.9	7.6[1]
Fat . . .	1.2	1.6	3.7	4.8	6.9	17.1	3.1	3.2	43.8
Sugar of milk .	5.7	6.0	4.9	4.5	4.9	2.8	5.6	5.6	—
Ash	0.4	0.5	0.7	0.8	0.9	1.5	0.8	0.8	0.5

ANALYSES OF ASH.

One Thousand Parts of Milk Contain—

	Man.	Dog.	Horse.	Cow.	Goat.	Sheep.
K_2O	0.780	1.41	1.05	1.77	2.35	1.17
Na_2O	0.232	0.81	0.14	1.11	0.52	1.08
CaO	0.328	4.53	1.24	1.60	2.10	2.72
MgO	0.064	0.20	0.13	0.21	0.36	0.50
Fe_2O_3	0.004	0.02	0.02	0.004	0.015	0.04
P_2O_5	0.473	4.93	1.31	1.97	3.22	4.12
Cl	0.438	1.63	0.31	1.70	2.04	1.34

The composition of the milk in various mammals is thus very striking in its variability. So far as I know, no attempt has been made to explain this difference. It appears to me that a teleological explanation may be found in the different rate of growth of the sucklings. It is a plausible conjecture that a more rapidly growing animal needs a milk richer in those constituents which serve particularly to build up tissue—proteid and inorganic salts. This connection appeared in the analyses of milk [2] which I published in 1874.

One Hundred Parts of Milk Contained—

	Proteid.	Ash.
Human	1.4	0.22
Horse	1.8	0.41
Cow	4.0	0.80
Dog	9.9	1.31

Nos. I., II., and III. It speaks well for these figures that, although obtained by very different methods, they all agree well with each other. The analyses of the ash are obtained from G. Bunge, *Zeitschr. f. Biolog.*, vol. x. p. 295: 1874; and from Fr. Pröscher, *loc. cit.*

[1] Proteids and sugar of milk.

[2] G. Bunge, *Zeitschr. f. Biolog.*, vol. x. p. 295: 1874.

Now it is well known that the infant grows more slowly than the foal, the foal than the calf, the calf than the dog. In order to see whether this theory held good universally I suggested to Mr. Pröscher that he should estimate the rapidity of growth of the domestic animals during lactation, as so far the weights at different periods had only been ascertained in the case of infants, foals, and calves.[1] In the following table I give the results of these weighings as well as the most reliable average figures of the proteid and ash of the milk. Of the constituents of the ash, the amounts of phosphoric acid and lime are particularly mentioned, since these substances are especially concerned in the building up of the tissues. The alkaline chlorids stand in a different position, and play an important part in excretion.[2]

One Hundred Parts of Milk Contain—

Time in which the body-weight of the new-born animal was doubled.	Proteid.	Ash.	Lime.	Phosphoric acid.
Man 180 days	1.6	0.2	0.328	0.473
Horse . . 60 "	2.0	0.4	1.24	1.31
Cow . . . 47 "	3.5	0.7	1.60	1.97
Goat . . 19 "	4.3	0.8	2.10	3.22
Pig . 18 "	5.9	—	—	—
Sheep 10 "	6.5	0.9	2.72	4.12
Dog . . . 8 "	7.1	1.3	4.53	4.93
Cat . . . 7 "	9.5	—	—	—

These results thus confirm in a striking manner the suggestion which was put forward above. The agreement would perhaps be still more complete if the specimens of milk analyzed had all been taken at the time that the weight was first doubled. A sample of the milk should be analyzed every day from the date of birth until that on which the weight was doubled, and the average of these analyses taken. For instance, the amount of proteid and ash in the milk diminishes with the duration of lactation. The suckling grows the most rapidly directly after birth, and increases in weight by degrees more and more slowly. The composition of the milk varies in accordance with the growth. The same law which we have laid down in the case of the various mammals also holds good for the various stages of development in the individual. My attention was directed to their connection by

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[1] Fr. Pröscher, *Zeitschr. f. Biolog.*, vol. xxiv. p. 285: 1897.

[2] Compare the agreement in the composition of the ash of milk and that of the suckling discussed in the last chapter.

an analysis of milk published in 1874. Thus in one woman during the first month after birth the milk contained 15 per mille proteid, whereas in the tenth month the amount had dropped to 9 per mille; the proportion of ash having likewise decreased.[1] The diminution of proteid in the milk as lactation proceeds has also been observed and tabulated by other authors for man and animals.[2]

It has long been known that the proportion of proteid in milk is very large from the first to the third day after birth, and this may be recognized without any quantitative estimation from the fact that this milk, to which the name of colostrum has been given, coagulates on boiling. As a practical result of this fact, a wet nurse can never completely replace the mother unless her infant has been born on the same day as her foster child.

As regards the remarkable difference in the amounts of fat and sugar in the milk of various animals, we might anticipate that here climate might have the same influence that we have seen it to possess for the food of man in cold and hot countries. As already mentioned, people in cold regions instinctively adopt a diet rich in fat and poor in sugar, while the converse is the case among the inhabitants of warm countries. Correspondingly we find the milk of animals which originally lived in a warm climate, rich in sugar and poor in fat (camel, llama, horse, donkey), while the milk of animals inhabiting the North is rich in fat and poor in sugar (reindeer). The composition of human milk shows that the human race was cradled in the warmer regions of the earth and supports a hypothesis which is based on many other grounds. The exception to this rule, *e. g.*, the higher percentage of fat in the milk of the elephant, a native of southern climes, may be more apparent than real. It is possible that the elephant may be descended from a northern ancestor, since the mammoth is known to have lived during the diluvial period in the present home of the reindeer. The elephant may therefore have emigrated southwards and have partially preserved the original composition of the milk. A thorough comparative analysis of the milk of all mammals may perhaps be the means in the future of controlling all the conclusions which have been arrived at by comparative anatomists, paleontologists, systematists, and natural historians.

The high percentage of fat in the milk of the dolphin

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[1] G. Bunge, *loc. cit.*, pp. 316 and 317.

[2] Th. Brunner, Pflüger's *Arch.*, vol. vii. p. 440: 1873; Siedamgrotzky u. Hofmeister, *Mitth. a. d. chem. physiol. Versuchsst. d. Thierarzneischule in Dresden*, 1879. H. Weiske u. G. Kennepohl, *Journ f. Landw.*, vol. xxix. p. 451: 1881.

(*Globiocephalus melas*) (three times as much as in that of the reindeer) may be explained on two grounds, firstly, that it lives in high latitudes, and secondly, that, being an aquatic animal, it is surrounded by a better conductor of heat than is the case with animals that live on land, and so needs for the maintenance of its temperature a higher proportion of the food-stuff with the greatest potential energy, *i. e.*, fat.

The great amount of fat in the milk of guinea-pigs cannot be explained in this way, since these animals come originally from a tropical country—Peru. From the first day of birth the guinea-pig picks up its own food by the mother's side. The milk in this case plays but a secondary part therefore in its nutrition, and only supplies a welcome addition to the vegetable food so deficient in fat.

These observations show how carefully nature has provided for the supply of all necessary food-stuffs in their due proportions. It is therefore not a matter of indifference whether the young derives its nourishment from its own mother or from the milk of another animal, or even from an artificial food. Even were the constituents and their proportions in the milk known to us, the preparation of such an artificial food would present considerable difficulties. But we must acknowledge that we are possibly not even acquainted with all the constituents. For instance, the various proteids and nucleins of milk have not yet been separated out as chemical entities, nor have their characteristics in this condition been studied. And finally there is the possibility that milk may contain small amounts of substances not yet discovered, which may nevertheless play an important part in nutrition.

Now in consequence of the degeneration of our race and as a result of the indifference of many mothers, the necessity for the artificial rearing of infants frequently arises.

A glance at the table on p. 106 shows that if cow's milk be diluted with an equal volume of water the amount of proteid is nearly the same as in human milk. The total ash is only slightly higher; the quantity of lime however is two and a half times, that of phosphoric acid twice as great. The smaller proportion of sugar and fat can be supplied by the addition of sugar of milk and cream.

Instead of a solution of sugar of milk, cow's milk is sometimes diluted with solutions of other forms of sugar as well as with starchy decoctions from all kinds of cereals.[1] Which

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[1] An account of the comprehensive literature on the subject of the artificial feeding of infants is given by Ph. Biedert, "Die Kinderernährung im Säuglingsalter," 3d edit., Stuttgart, 1897, and by E. Feer, *Jahrb. f. Kinderheilk.*, N. F., vol. xlii. p. 195: 1896.

of these is the more digestible for infants it is difficult to decide owing to individual variations; hence for the present no rule can be laid down, especially as no trustworthy statistics are available on this subject.

Experience however shows that many children are incapable of digesting any form of diluted cow's milk, and that in no case does it completely replace the mother's milk.

What are the reasons for this fact?

1. The caseinogen of human milk is not identical with that of cow's milk, as is shown by the varying proportion of phosphorus and sulphur. The caseinogen belongs to the so-called nucleo-albumins, *i. e.*, to the substances which on artificial digestion split up into peptone and a substance resembling nuclein. The caseinogens therefore invariably contain considerable amounts of phosphoric acid as well as some lime. According to Lehmann and Hempel[1] the percentage of phosphate of lime in the caseinogen of human milk is 3.2, and in cow's milk 6.6. The proportion of sulphur in the two cases is 1.1 per cent., and 0.72 per cent.

A complete and accurate analysis of cow's caseinogen has been made by Hammarsten.[2] This may be compared with the analysis of the caseinogen of human milk, which was carried out by Wroblewski[3] under Drechsel's guidance.

Caseinogen.

	From cow's milk.	From human milk.
C	52.96	52.24
H	7.05	7.32
N	15.65	14.97
S	0.74	1.11
P	0.84	0.68
O	22.78	23.66

2. By the action of rennet ferment[4] in the stomach, the

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[1] Jul. Lehmann u. W. Hempel, Pflüger's *Arch.*, vol. lvi. p. 574: 1894.

[2] Hammarsten, *Zeitschr. f. physiol. Chem.*, vol. vii. p. 269: 1883; and vol. ix. p. 296: 1885.

[3] A. Wroblewski, "Beitr. zur Kenntniss des Frauenmilchcaseins u. seiner Unterschiede vom Kuhcasein." Dissert., Bern, 1894.

[4] The significance of rennet ferment and of casein coagulation in the stomach is still unexplained. For a knowledge of the experiments which have been made with a view to the elucidation of this problem I recommend: Hammarsten, Upsala läkareförennings Förhandlingar, 8, p. 63: 1872; 9, pp. 363 and 452: 1874 (complete account in Maly's *Jahresber. f. Thier Chemie*). "Zur Kenntniss des Caseins u. der Wirkung des Labferments," Upsala, 1877. *Hoppe-Seyler's Zeitschr.*, vol. xxii. p. 103: 1896. Alex. Schmidt, "Beitr. z. Kenntniss der Milch," Dorpat, 1874. M. C. du Saar, "Melkstremmende werking van den maaginhoad bij jonge zuigelingen.," Diss., Amsterdam, 1890. M. Arthus et C. Pagès, *Arch. de Physiol.*, 1890, pp. 331 and 540. *Mém. soc. biol.*, vol. xliii.

caseinogen of human milk coagulates in fine floccula, that of cow's milk in coarse lumps, which by many children cannot be digested. If the cow's milk be diluted with a solution of milk-sugar, the coarse precipitation is prevented. Although by such means it is possible to avoid the aggregation of the precipitate into solid lumps, this clot still remains closer, tougher, and more indigestible than that of human milk. This seems to depend on the greater percentage of lime and the smaller alkalinity of cow's milk. As Soxhlet[1] has clearly pointed out, any attempt to get rid of these differences is beset with great difficulties, which at present are in practice almost insuperable.

It might have been anticipated that better results would be obtained if instead of cow's milk the milk of some animal which in its composition more closely resembled human milk were employed. A glance at the Table on p. 105 shows that this is especially the case with mares' and asses' milk. But so far we have too slight a practical experience to argue upon.

3. To add to the other difficulties of artificial feeding there remains the necessity for sterilization. Milk is a most fertile nutrient medium for all kinds of microörganisms, which increase in it at an incredible rate. Fresh milk, which contained 9000 bacteria in one c.cm. when first brought into the laboratory, showed an hour later 31,750; after nine hours, 120,000; and after twenty-four hours, 5,600,000.[2]

A short exposure to the boiling temperature does not suffice to destroy all bacteria. If still higher temperatures be employed, the sugar is attacked and causes the milk to become brown. For the best method of approximately sterilizing milk without greatly impairing its nutritive value, the reader may be referred to the latest accounts in the works of P. Cazeneuve,[3] L. Fürst,[4] A. Baginsky,[5] and a summary of the literature by Biedert, *loc. cit.*

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p. 131: 1891. Zdzislaw Szydlowski, *Prager med. Wochenschr.*, No. 32: 1892. Pagès, *Comptes rendus*, vol. cxviii. p. 1291: 1894. R. Peters, "Das Lab u. die Labähnlichen Fermente." Gekrönte Preisschrift, Rostock, 1894. M. Arthus, *Arch. de Physiol.*, vol. xxvi. p. 257: 1895. A. Edmunds, *Journ. of Physiol.*, vol. xix., Nos. 5 and 6: 1896. F. S. Locke, *The Journ. of Experimental Med.*, vol. ii., No. 5: 1897.

[1] F. Soxhlet, "Die chem. Unterschiede zwischen Kuh u. Frauenmilch u. die Mittel zu ihrer Ausgleichung." Vortrag gehalten am 11. Jan. 1893. *Münch. med. Wochenschr.*, 1893. Compare O. Heubner, *Berliner klin. Wochenschr.*, vol. xxxvii. pp. 841 and 870: 1894.

[2] Miquel, *Journ. de Pharm. et de Chim.*, vol. xxi. p. 565: 1890. Compare E. v. Freudenreich, *Milchzeitung*, p. 33: 1890.

[3] P. Cazeneuve, *Bull. de la Soc. chim. de Paris*, vol. xiii. p. 502: 1895.

[4] L. Fürst, *Deutsche Medicinalzeitung*, p. 1007: 1895.

[5] A. Baginsky, *Berliner klin. Wochenschr.*, No. 18: 1895.

4. Finally with anything but the mother's milk there is the constant danger of over-feeding the infant. When taking the breast, the fatigue consequent upon the effort of sucking appears to prevent the infant taking more than the proper amount, whereas from the feeding bottle, which can be drawn without effort, the infant takes more than it can digest, with consequent dyspepsia.[1]

From these remarks it will readily be seen that artificial feeding is fraught with grave danger.

If on the one hand we observe how carefully nature has adapted the composition of milk to the needs of every species of mammal, and if on the other we consider how ignorant we are concerning the nature of the food-stuffs, the digestive processes in the infant and the disturbances which these are liable to from the myriad microörganisms in the intestines, it is not a matter for wonder that in spite of the greatest efforts the natural diet for infants has not so far been successfully replaced by any artificial food. In support of this contention we may quote the following statistics:—

In 1890 49,362 children were born alive in Berlin. Before the end of their first year 12,623 of these children had died. Of these—

1588 had been fed at the breast;
8008 had been fed with cow's milk.

The remaining infants had been brought up on milk and artificial foods, or upon these latter alone. No deduction however can be drawn from the influence of the food on the mortality unless we know what proportion of the whole number of children born were reared at the breast. The following figures enable us to form an approximate idea. The census taken December 1, 1890, showed that there were then in Berlin 39,312 children under the age of one year. Of these—

20,812 were breast-fed;
16,620 were reared by hand.

Therefore of the breast-fed children one in thirteen died; whereas of those brought up by hand the mortality rose to one out of every two infants.

No doubt this excessively high rate of infant mortality is due not only to the unnatural mode of diet, but partly to the neglect which is doubtless in many cases associated therewith; since a mother who nurses her child would also, as a general rule, instinctively lavish more care upon it.

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[1] E. Feer, *loc. cit.*, p. 196.

The mortality among children reared on artificial foods is much higher even than among those fed on cow's milk.[1]

Heathen races have frequently sanctioned infanticide. Christian races torture their children slowly to death. Artificial feeding was unknown to the ancients.[2]

When children are breast-fed, the condition of the mother's health acts both on the quantity and the quality of the milk secreted.[3] But the quality of the milk seems to be but little dependent upon the nature of the diet. Occasionally an increase of fat is observed after very abundant feeding; but the amount of the other constituents in the milk is hardly altered.

Taking milk as our starting point, let us now proceed to consider the diet normally required by the adult. In the case of the infant we are acquainted with the natural composition of the food; we can also ascertain the exact quantity provided by nature by weighing the infant before being placed at the breast and again after it has instinctively satisfied its hunger. The difference in weight gives the amount of milk taken, and the repetition of this process at each meal gives the total amount for the twenty-four hours.

The most recent and exact estimates of this kind have been carried out by E. Feer.[4] He determined the amount taken by a boy from birth until the 30th week, and found that in the last week he took 951 grms. of milk daily. At this time the child's weight was 8226 grms. From the average composition of human milk, *viz.*:—

Proteid	1.6 per cent.
Fat	3.4 "
Sugar	6.1 "
Ash	0.2 "

we can compute the absolute amount of the nutriment daily taken in—

Proteid	15.2
Fat	32.3
Sugar	58.0
Ash	1.9

Statistisches Jahrbuch der Stadt Berlin. Doppeljahrgang xvi., xvii. Statistik der Jahre 1889 und 1890, pp. 30 and 148: Berlin, 1893.

[2] Biedert, *loc. cit.*, p. 155.

[3] An account of the very comprehensive literature on this subject is given by Biedert, *loc. cit.*, chap. iii.

[4] The latest experiments concerning the influence of the food on the composition of human milk are those of P. Baum ("Die Frauenmilch," Sammlung klinischer Vorträge von Volkmann, No. 105, p. 202, *et seq.*, Leipzig, 1894). The earlier literature is here quoted. Experiments on animals have given essentially the same results. For the extensive literature on this subject the text-books on agriculture should be consulted.

According to the same proportions a man of 70 kilos. would take in—

Proteid	129
Fat	275
Sugar	494
Ash	16

These figures agree very well with the observations which have been made directly on the adult. I have already mentioned that a man in full work, who can procure sufficient food for himself, eats daily—

Proteid	100–150
Fat	50–200
Carbohydrates	300–800

It might be thought that the amount of proteid for the adult reckoned from that required by the infant would be a maximum value, since the young animal needs larger quantities of proteid for the growth of its tissues, whereas the man has only to maintain his existing store. But it must be remembered that the sexual functions of the adult are likewise a form of growth—"growth beyond the boundaries of the individual." This growth of the tissues in man consists in the production of spermatozoa, in woman in the development of the embryo or the formation of menstrual fluid. The growth beyond the boundary of the individual appears in women during the child-bearing period to be only in abeyance during the time of lactation, when the milk with its rich complement of proteid is secreted. But the secretion of milk may be regarded as a growth of tissue, since as a matter of fact the fat-laden epithelial cells of the mammary glands either partially or completely break up and are regenerated.[1]

But the amount of fat (275 grms.) calculated for the adult from that required by the infant is certainly too high. The infant has relatively a much larger body-surface and therefore gives off more heat; it thus requires larger quantities of the food-stuff that produces the greatest heat in its combustion.

The figure 494 for the carbohydrates agrees very well with the mean numbers obtained in direct experiments on adults. A young man eighteen years of age who took nothing but

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[1] The latest researches on the histological processes involved in the secretion of milk are those of F. Nissen, *Arch. f. mikr. Anat.*, vol. xxvi. p. 337: 1886. E. Coen, *Beitr. z. pathol. Anat. u. Physiol.* v. Ziegler u. Nauwerck, vol. ii. p. 83: 1887. P. R. Kadkin, Diss. Petersburg: 1890 (in Russian). Frommel, *Arch. f. Gynäk.*, vol. xl., Hft. ii.: 1891; and *Centralbl. f. Gynäkol.*, p. 471: 1891. J. Steinhaus, *Du Bois' Arch.*, Physiol. Abth. Supplementband, p. 54: 1892.

cow's milk (compare the conclusion of Lecture XXV.) drank three liters a day, containing—

Proteid	105
Fat	111
Sugar	147
Ash	21

His state of nutrition was certainly bad and his powers of work poor. But it cannot be decided whether this should be referred to an insufficient income of some organic food-stuff or merely to the absence of iron. (See Lecture XXV.)

LECTURE IX

SUBSIDIARY ARTICLES OF DIET

MAN, together with all animals, consumes certain articles which are neither sources of energy nor possessed of reparative power for the continual body waste. They are eaten on account of the agreeable influence which they exert on the nerves of taste or smell or on other parts of the nervous system. We call these substances condiments and stimulants. They are as necessary to us as the food-stuffs themselves.

It is a very noticeable fact that our most important organic food-stuffs are absolutely without taste or odor. We can only smell volatile matter, or taste such substances as are soluble in water. Our organic food-stuffs have neither of these properties. They are not in the least volatile, and are almost all insoluble in water. Fats, as we well know, are not miscible with water, and proteids only swell without actually dissolving in it. Of the carbohydrates, the sugars alone are soluble, and they taste sweet. In the case, then, in which food is possessed of any taste at all, it is agreeable. Since the bulk of our food can produce no effect on our organs of sense, we find our organs of taste and smell so adapted that the volatile and soluble matters, which are constantly associated with aliments as they occur in nature, produce agreeable sensations when they act on these sense-organs. These sensations not only increase our desire for food; they also help digestion. It is a matter of common experience, that even the imagination of fragrant and savory food may augment the secretion of saliva. The increased secretion of gastric juice produced by the same cause has been observed on dogs with a gastric fistula. To show them from a long distance a piece of meat is sufficient to excite the secretion of the gastric juice. Thus, if a gastric fistula be established in a dog, and at the same time the esophagus be divided, so that all food taken in by the mouth falls out by the opening in the esophagus without reaching the stomach, it is observed that every act of taking food by the mouth causes a large secretion of gastric juice containing both hydrochloric acid and pepsin, although the food does not reach the stomach. This reflex secretion is abolished by division of both vagi.[1] It is hence probable that the activity of all other glands associated with digestion is reflexly aroused by agreeable tastes and smells, and that all processes and movements which are involved in digestion and absorption are hereby assisted. Pleasant sensory impressions produce a cheerful frame of mind, and thus indirectly tend to act favorably on all the processes of the body. On the other hand it is a familiar fact that disagreeable smells and tastes cause a disturbance of digestion which may even induce vomiting. The necessity of these adjuncts to food is then beyond doubt; every effort to consume food which has neither taste nor smell would soon fail.

Whilst animals merely take such sapid substances as occur naturally mixed with the food they eat, man goes much further by artificially separating the subsidiary from the necessary aliments. He takes the former by themselves, or with only a small proportion of the latter. Hence arises for man the danger of excess. The regulating mechanism, which in animals consists of the feeling of satiety which sets in as soon as they have eaten enough, tends to be disturbed. So long as only the senses of taste and smell are concerned, there is but little danger of excess. The more intense the stimulation of the organs of smell and taste, the more rapidly is the sensibility of our nerves blunted; we get tired of the impressions made upon them. But besides those substances which act agreeably on our senses, man has learnt to isolate others which produce pleasurable sensations by their action on the functions of the brain; these we term narcotics. He has discovered them even when they cannot be detected by smell or taste, and when they occur only in plants which have no nutritive value; such are opium, tea, coffee, hashish, &c. Others, which nature does not produce, he has learnt to prepare artificially from innocuous substances, as for instance alcohol from sugar. Conscious volition disturbs the harmonious action of the unconscious instincts, and becomes the source of unlimited misery.

So long as we are unacquainted with the chemical processes by which these subsidiary articles of diet act on the nervous system, their special consideration is a subject rather for toxicology and the physiology of the nervous system than for physiological chemistry. I shall therefore treat of only a few which are still often considered to be true aliments. The most important of these are alcoholic drinks.

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[1] J. P. Pawlow and E. O. Schumowa Simanowskaja, Du Bois' *Arch.*, p. 53, 1895.

We know that ALCOHOL is to a very great extent oxidized in the body. Only a small part is excreted unchanged by the kidneys and lungs.[1] Alcohol is therefore without doubt a source of energy when absorbed into the body. But it does not therefore follow that it is a food. To prove this it would be necessary to show that the energy liberated by the oxidation of alcohol is used to aid the performance of a normal function. It is not enough that chemical potential energy is transformed into kinetic energy; the transformation must occur at the right time, in the right place and in definite parts of the tissues. The tissues are not so constituted that they can be fed with any and every combustible material; we do not know, for instance, whether alcohol can serve as a source of the energy by virtue of which the functions of muscle and nerve are performed (see Lecture XXIII.).

It will be objected that the heat which is produced by the combustion of alcohol must in any case be useful to our organism. Even if it does not directly subserve any definite function of a particular organ, the combustion of the alcohol must economize the consumption of other food-stuffs. But even this cannot be admitted. For whilst on the one hand the alcohol increases the production, on the other it increases the loss, of heat. Owing to the paralyzing action which it exerts on the vasomotor system, a dilatation of the vessels, and especially of the cutaneous vessels, occurs, and consequently there is an increased loss of heat. The total result is a diminution of the temperature of the body, which has been actually proved to take place.

Alcohol has invariably a paralyzing influence. All the results which, on superficial observation, appear to show that alcohol possesses stimulant properties, can be explained on the ground that they are due to paralysis.[2]

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[1] Vict. Subbotin, *Zeitschr. f. Biolog.*, vol. vii. p. 361: 1871; Dupré, *Proc. Roy. Soc.*, vol. xx. p. 268: 1872; and *The Practitioner*, vol. ix. p. 28: 1872; Anstie, *Practitioner*, vol. xiii. p. 15: 1874; Aug. Schmidt, *Centralbl. f. d. med. Wissensch.*, No. 23, 1875; H. Heubach, "Ueber die Ausscheidung des Weingeistes durch den Harn Fiebernder," Dissert.: Bonn, 1875; C. Binz, *Arch. f. exper. Path. u. Pharm.*, vol. vi.: 1877; H. Heubach, "Quantitative Bestimmung des Alkohols im Harn," *Arch. f. exp. Path. u. Pharm.*, vol. viii. p. 446: 1878; G. Bodländer, Pflüger's *Arch.*, vol. xxxii. p. 398: 1883.

[2] With regard to this matter, we recommend the perusal of the short and lucid description in Schmiedeberg's "Grundriss der Arzneimittellehre," 2d edit., pp. 25, 27: Leipzig, Vogel, 1883. Compare Zimmerberg, Dissert., Dorpat, 1869. Maki, Dissert., Strassburg, 1884. H. Dreser, "Arch. f. exper. Path. u. Pharm.," vol. xxvii. p. 87: 1890. P. v. d. Mühll and A. Jaquet, *Correspondenz-blatt f. schweizer Aerzte*, No. 15, p. 457, 1891, and E. Kræpelin, "Ueb. d. Beeinflussung einfacher psychischer Vorgänge durch einige Arzneimittel. Jena, Fischer, 1892; A. Smith, *Bericht üb. d. V. internat. Congress z. Bekämpfung des*

It is a common idea that alcohol produces a warming effect in cold weather. This feeling of warmth depends, in the first place, on the fact already noticed—that the paralysis of the central nervous system causes an increased blood-supply to the surface of the body; and secondly, in all probability, on the blunting of the sensibility of the central organs which are concerned in the sensation of cold.

The stimulating action which alcohol appears to exert on the psychical functions is also only a paralytic action. The cerebral functions which are first interfered with are the powers of clear judgment and criticism. As a consequence, emotional life comes into free play unhampered by the guiding-strings of reason. The individual becomes confiding and communicative; he forgets his cares and becomes gay; in fact, he no longer clearly sees the dangers and difficulties of life. But the most pronounced paralyzing action of alcohol is seen in the way it allays all sorts of discomfort and pain, and, above all, the worst sort of pain—mental suffering, anxiety, and trouble. Hence the light-heartedness which prevails at a carouse. It is a prejudice which depends upon self-deception, to believe that a man ever becomes witty by aid of spirituous drinks. This error is simply one of the results of the paralytic influence mentioned above; as the power of criticising one's self diminishes, self-complacency increases. The lively gesticulations and useless exertions of intoxicated people are due to paralysis, the inhibitory influence, which prevents a sober man from uselessly expending his strength, being removed. Associated with this is the increased frequency of pulse, which is commonly cited as an instance of the stimulating power of alcohol; it has nothing to do with the action of alcohol, but is caused by the surroundings among which the alcoholic drinks are generally taken. It is a consequence of the excited condition, and, according to the experiments hitherto made, does not occur when the body remains quiet.[1]

A paralytic symptom, which is erroneously regarded as one of stimulation, is also found in the deadening of the sense of fatigue. There is a strong belief that alcohol gives new strength and energy after fatigue has set in. The sensation of

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Missbrauches geistiger Getränke, Basel, p. 341: 1896; C. Fürer, *ibid.*, p. 355; G. Aschaffenburg, "Psychologische Arbeiten v. E. Kræpelin," vol. i. p. 608: 1896. C. Binz ("Der Weingeist als Heilmittel," Sonderabdruck aus den *Verhandlungen des VII. Congresses f. innere Medicin zu Wiesbaden*, 1888: Wiesbaden, Verlag von J. F. Bergmann, 1888) upholds the older view, according to which alcohol has a stimulating action when taken in small doses.

[1] Schmiedeberg, *loc. cit.*, p. 26; Zimmerberg, "Unt. üb. den Einfluss des Alkohols auf die Thätigkeit des Herzens," Dissert., Dorpat, 1869. P. v. d. Mühll and A. Jaquet, *Correspondenzblatt f. schweizer Aerzte*, p. 457: 1891.

fatigue is one of the safety-valves of our machine. To stifle the feeling of fatigue in order to be able to work on, is like forcibly closing the safety-valve so that the boiler may be overheated.

That this prejudice concerning the 'strengthening' power of alcohol maintains so firm a hold is to be explained by the experiences of habitual drinkers. Any one who is in the regular habit of taking a considerable quantity of alcohol is better able to do his work while he continues it than if he were suddenly to leave it off. We cannot at present explain this result, although it is quite analogous to the effect of other narcotics on persons who have been accustomed to their use. The opium-eater can neither work, nor eat, nor sleep, if his opium be denied him; he is 'strengthened' by the opium. But a man who is not accustomed to a narcotic is most certainly not rendered more fit for work by taking it.

The uselessness, if not harmfulness, of even moderate doses of alcohol rests on better evidence than scientific deductions and experiments. In connection with the sanitation of armies, thousands of experiments upon large bodies of men have been made, and have led to the result that, in peace and war, in every climate, in heat, cold, and rain, soldiers are better able to endure the fatigues of the most exhausting marches when they are not allowed any alcohol at all.[1] A similar result is observed in the case of the navies, and on thousands of merchant vessels belonging to England and America, which put to sea without a drop of alcohol. Most whalers are manned by total abstainers.

That mental exertions of all kinds are better undergone without alcohol is generally admitted by most people who have made the trial. Alcohol then makes no one stronger; it only deadens the feeling of fatigue.

One of the disagreeable sensations which alcohol diminishes is that of boredom. This feeling is, however, like the sensation of fatigue, one of the arrangements for self-regulation which the organism possesses. Just as the feeling of fatigue makes us rest, so the feeling of boredom encourages us to exertion, without which nerve and muscle atrophy. It is interesting to observe what curious means a lazy and empty-headed man adopts in order to be free from the demon of boredom without making personal exertion. It drives him without rest from place to place, to this company and that, from one distraction to another. But all these attempts to escape from himself

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[1] See A. Baer, "Der Alkoholismus," pp. 103–108: Berlin, 1878. References to the original works are given here.

would be in vain, and the bulk of mankind would be driven to exercise their brain and muscles in some way or another, in order to obtain the feeling of rest and satisfaction and to lose their sense of tedium, were it not for alcohol. Alcohol frees them easily and agreeably from this demon. A drinker is never conscious of his own emptiness. He wants no interests and ideas; he has the comfort and satisfaction of narcosis. There is nothing so dangerous to the development of a man, nothing which so undermines his character, nothing which so surely destroys the remaining energy he is capable of, as the continual deadening of the sense of tedium by means of alcohol.

Another point which is adduced in favor of alcoholic drinks is that they slow metabolic processes. It is true that a slight diminution in the excretion of nitrogen, and consequently of proteid decomposition, is observed after moderate doses of alcohol.[1] But it is difficult to understand why this should be made a reason for recommending alcoholic drinks. Why should we wish to diminish the metabolism of the body? Is not metabolism, or the breaking down of the tissues, the source of all our energy? The intensity of this metabolism, this conversion of potential into kinetic energy, is constantly regulated by a complicated nervous mechanism, which now acts in an inhibitory, now in an accelerating direction, according to the requirements of the various organs. To interfere with this self-controlling mechanism by the action of poisonous substances can hardly be wise, since we are almost entirely in ignorance concerning its intimate character. What means have we of judging whether the metabolism is too quick or too slow?

Moreover the latest and most accurate researches on man have failed to show any economy of proteid as the result of the injection of alcohol.[2] Among these investigations the minutely accurate experiments of Miura upon himself are especially worthy of mention. This observer, after bringing himself into a condition of nitrogenous equilibrium on a diet of fat and carbohydrate, replaced for a few days a portion of the carbohydrate by an equivalent quantity of alcohol. He found that, on these days, there was a rise in the excretion of nitrogen, which was as great as on other days when a portion of the

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[1] A. P. Fokker, "Nederlandsch Tijdschrift voor Geneeskunde," p. 125: 1871; Imm. Munk, *Verh. der Physiol. Ges. zu Berlin:* Jan. 3, 1879; L. Reiss, *Zeitschr. f. klin. Med.*, vol. ii. p. 1: 1880.

[2] Parkes, *Proc. Roy. Soc.*, vol. xx. p. 402: 1872. H. Keller (Bunge's laboratory), *Zeitschr. f. physiol. Chem.*, vol. xiii. p. 128: 1888. Stammreich, "Ueb. d. Einfluss d. Alkohols auf d. Stoffwechsel d. Menschen," Dissert.: Berlin, 1891. K. Miura, *Zeitschr. f. klin. Med.*, vol. xx. p. 137: 1892.

carbohydrate was omitted without any corresponding food to take its place. He came to the conclusion therefore that alcohol had no influence on proteid disintegration, and that it could not replace carbohydrate as a sparer of proteid.

In large doses alcohol increases instead of diminishing the excretion of nitrogen.[1] In this respect it resembles certain powerful poisons, especially phosphorus and arsenic, which cause increase in the excretion of nitrogen, but at the same time diminish the amount of oxygen taken up and carbonic acid excreted, and consequently produce fatty degeneration of various organs. It appears that these poisons give rise to the production of fat from proteid; the nitrogen, with a small quantity of the carbon, is separated from the proteid molecule, and the residue, free from nitrogen, is stored up in the tissues as fat. We shall have to consider this process in greater detail in a later section (Lecture XIV.). Possibly the fatty degeneration of the organs sometimes observed in drunkards is to be referred to a similar action. But unfortunately the experiments hitherto made have not decided whether the consumption of alcohol has any influence on the elimination of carbonic acid.[2]

It is commonly thought that alcoholic drinks act as aids to digestion. In reality it would appear that the contrary is the case. Any one may make the observation on himself, that a meal without alcohol is more quickly followed by hunger than when alcohol is taken. The inhibitory influence of alcohol on digestion has been observed on a patient with a gastric fistula,[3] on several other persons by the aid of the stomach-pump,[4] and by means of numerous other experiments.[5]

Up to this point I have chiefly considered the action of alcohol on persons who are usually called moderate drinkers. To describe the ultimate consequences of excessive drinking can hardly come within the scope of these lectures. It may be mentioned, however, that the misuse of alcoholic drinks causes

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[1] Imm. Munk, *loc. cit.*

[2] The oft-quoted experiments of Boeck and Bauer allow of no definite conclusion, as the duration of the experiments was too short (*Zeitschr. f. Biolog.*, vol. x. p. 361: 1874). The same is still more applicable to the experiments of Wolfers (*Arch. f. d. gesam. Physiol.*, vol. xxxii. p. 222: 1883). Zuntz and Berdez, *Du Bois' Arch.*, p. 178: 1887. J. Geppert, *Arch. f. exper. Path. u. Pharm.*, vol. xxii. p. 367: 1887. N. Simanowski and C. Schoumoff have shown that absorption of alcohol diminishes the oxidation of benzol into phenol (Pflüger's *Arch.*, vol. xxxiii. p. 251: 1884).

[3] F. Kretschy, *Deutsch. Arch. f. klin. Med.*, vol. xviii. p. 527: 1876.

[4] W. Buchner, *ibid.*, vol. xxix. p. 537: 1881.

[5] Emil Schütz, *Prager med. Wochenschr.*, No. 20: 1885; Bikfalvi, Maly's *Jahresber. f. Thier Chemie*, p. 273: 1885; Massanori Ogata, *Arch. f. Hygiene*, vol. iii. p. 204: 1885; Klikowicz, Virchow's *Arch.*, vol. cii. p. 360: 1885.

a whole host of diseases; that no organ of our body remains free from its injurious action.[1] It is also apparently certain that from 70 to 80 per cent. of crime, and from 10 to 40 per cent. of the suicides in most civilized countries, are to be ascribed to alcohol.

We must however strictly discriminate between the use of alcohol as a luxury and an article of diet, and its use as a medicine. In the opinion of many practitioners, it is indispensable as a medicine. It is precisely its paralyzing properties which render it valuable in this case. It is a mild anesthetic, and acts as a sedative by diminishing abnormally increased reflex irritability. Alcohol is further used as an antipyretic; but proof of its value in this capacity is still lacking.

It is evident to every reasonable being that alcoholic drinks can only be prescribed for acute diseases, and should never be allowed in chronic disorders for the same reason that chloral and morphia are not given in such cases, unless indeed to compass euthanasia. There can be no doubt that many medical men are guilty of much harm in recommending the use of alcohol, and there is hardly a single drunkard who does not adduce the authority of some medical man or other in support of his failing. It is in the highest degree desirable that alcohol should be replaced by some other drug even in those cases where its use seems to be indicated, since it is hardly possible to get rid of the deeply rooted superstition as to the strengthening and stimulating effect of alcohol, so long as it continues to be constantly employed as a therapeutic agent. We may hope that the temperance hospitals which have been founded in England and America, and where absolutely no alcohol is given, may soon furnish sufficient statistics to prove once and for all that alcohol is not indispensable in medical practice.

TEA and COFFEE are much less likely to cause ill effects than alcoholic liquors. They exert no paralytic influence; on the contrary, they are helpful in both mental and physical exertions. In their use there is but little danger of excess. It is true that they occasionally disagree with certain people,

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[1] On this point see Legrain, "Hérédité et Alcoholisme," Paris, 1891; Laurent, "Les habitués des Prisons de Paris," Paris, 1890; P. Garnier, "La Folie à Paris," Paris, 1890; Bourneville, "Progrès médical," p. 21: 1897. J. Sendtner, "Ueb. Lebensdauer u. Todesursache b. d. Biergerwerben. Ein Beitrag z. Ætiologie d. Herzerkrankungen," München, 1891; Demme, "Ueb. d. Einfluss d. Alkohols auf. d. Organismus d. Kindes," Stuttgart, 1891; A. Strümpell, "Ueb. d. Alkoholfrage v. ærztlichen Standpunkte aus.," *Berl. klin. Woch.*, p. 933: 1893.

especially if taken in too large quantities; and their long-continued misuse may cause illness. But in these cases there is but little difficulty in inducing the people so affected to abstain. A patient who is recommended seriously to refrain from taking too much tea generally does so; a patient who takes too much alcohol does not easily give it up. A man rarely becomes the slave of coffee or tea, and excessive drinking of tea and coffee never produces a state of moral irresponsibility, nor leads to the commission of crime.

Tea and coffee contain, as is well known, an active principle common to both, caffein or thein, which is closely related to xanthin, a crystalline substance rich in nitrogen, which enters in small quantity into all our tissues. We shall study xanthin in connection with the chemistry of the urine (Lecture XX.). Caffein is xanthin with three methyl groups introduced into its molecule, and it can be artificially prepared from these constituents.[1]

It is a very remarkable and surprising fact that people of the most different races, in all parts of the world, have succeeded in discovering caffein in the most varied plants. The Arabs found it in the coffee bean; the Chinese in tea; the natives of Central Africa in the cola nut (*Cola acuminata*); those of South Africa in bush tea, the leaves of a variety of Cyclopia; the natives of South America in Paraguay tea (*Ilex paraguayensis*), and in the seeds of *Paulinia sorbilis*, a Brazilian creeper; the Indians of North America in Apalache tea, the leaves of several varieties of ilex. This fact is the more remarkable as caffein can be detected neither by its taste nor smell. Also interesting is the close relation of this universally prized luxury to one of the constituents of our tissues. It is possible that the caffein molecule, in consequence of its similar constitution, has an affinity for the same tissue-elements in which xanthin is found, and that it plays an analogous though, in consequence of its more complex constitution, a modified part. This may explain the stimulating action which it possesses.

Caffein is mostly destroyed in the tissues of our body. Experiments[2] conducted in Dragendorff's laboratory in Dorpat

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[1] Emil Fischer, Liebig's *Annal.*, vol. ccxv. p. 253: 1882.

[2] Rich. Schneider, "Ueber das Schicksal des Caffeïns und Theobromins im Thierkörper, nebst Untersuchungen über den Nachweis des Morphins im Harn," Dissert.: Dorpat, 1884. Schutzkwer ("Das Caffeïn u. sein Verhalten im Thierkörper," Dissert.: Königsberg, 1883) found that, of 0.2 grm. of caffein subcutaneously injected into a dog, only 0.012 reappeared in the urine. Maly and Andreasch ("Studien über Caffeïn und Theobromin," *Monatshefte der Chem.*, May: 1883) found that, of 0.1 grm. administered internally to a small dog, 0.066 reappeared in the urine.

have shown that of the amount of caffein which is absorbed as the result of ordinary tea and coffee drinking—a cup of coffee contains about 0.1 grm. caffein, and the same amount is contained in from 2 to 10 grms. dry tea leaves—none passes into the urine. Caffein can be detected in the urine when 0.5 grm. caffein has been taken. Caffein has no influence on the proteid metabolism of the organism. Voit[1] has shown by careful observation that the amount of nitrogen excreted is neither increased or diminished by the use of caffein.

This is not the place to give a detailed account of the various modes of action of caffein; I must refer you to works on pharmacology. In addition to this common constituent, tea contains ethereal oils,[2] and in coffee certain aromatic substances are formed as the result of roasting; hence the difference of taste and action of these substances.

A substance chemically closely allied and of similar action to caffein is found in the COCOA BEAN. This is theobromin, a dimethyl-xanthin. In the seeds of *Paulinia sorbilis*, from which guarana paste, much liked in South America, is prepared, both these substances are united. Filehne[3] has recently studied the action of theobromin on muscle and on the central nervous system, and compared it with the action of xanthin and of caffein. He has arrived at the interesting result that the chemical series, caffein (trimethyl-xanthin), theobromin (dimethyl-xanthin), and xanthin present a corresponding series in their pharmacological action. A monomethyl-xanthin is at present unknown. The cocoa bean is not only a luxury, but also very valuable as nutriment; it contains half its weight of fat, and in addition about 12 per cent. of proteid. Chocolate might be very serviceable for military purposes. It is hardly possibly to carry food in a more concentrated form than in chocolate.

BOUILLON and EXTRACT OF MEAT, which is bouillon evaporated to a semi-solid consistence, afford the most harmless subsidiary aliments. The extractives of meat do not, so far as is known, exert the slightest narcotic influence. They act entirely on taste and smell. This agreeable effect can hardly be overestimated, but we must guard against supposing that

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[1] C. Voit, "Unt. üb. d. Einfl. des Kochsalzes, des Kaffees und der Muskelbewegungen auf den Stoffwechsel," pp. 67–147: München, 1860.

[2] A. Koch and E. Kræpelin ("Psycholog. Arb.," vol. i. p. 378: 1895) have investigated the effects of these ethereal oils and of the thein separately, and have found that the pleasant results of tea drinking must be referred to both constituents.

[3] Wilhelm Filehne, Du Bois' *Arch.*, p. 72: 1886. A summary of the earlier literature will also be found here. Comp. also Kobert, *Arch. f. exper. Path. u. Pharm.*, vol. xv. p. 22: 1882.

meat bouillon possesses strengthening and nourishing properties. In regard to this, the most delusive notions are entertained, not only by the general public, but also by medical men.

Until quite recently, the opinion was held that bouillon contained the most nutritive part of meat. There was a confused idea that a minute quantity of material—a plateful of bouillon can be made from a teaspoonful of meat-extract—could yield an effectual source of nourishment, that the extractives of meat were synonymous with concentrated food.

Let us inquire what substances could render bouillon nutritious. The only article of food which meat yields to boiling water is gelatin. It is well known that proteid is coagulated, on boiling, the glycogen of meat is rapidly converted into sugar, and this again into lactic acid. The quantity of gelatin is moreover very small ; for a watery solution which contains only 1 per cent. of gelatin forms a jelly on cooling. This certainly occurs in very strong soups and gravies, but never in bouillon. Bouillon therefore contains much less than 1 per cent. of gelatin. In preparing extract of meat, the quantity of gelatin is reduced as much as possible, because it is in a high degree liable to putrefactive changes, and therefore likely to interfere with the preservation of the preparation. The other constituents of bouillon are decomposition products of food-stuffs—products of the oxidations and decompositions which take place in the animal organism. They cannot be regarded as nutritious, because they are no longer capable of yielding any kinetic energy, or at most such a small amount that it is of no importance whatever.

Nevertheless, until the most recent times, creatin and creatinin,[1] which are among the chief constituents of meat-extract, were regarded as the source of energy in muscle. This assertion was shown to be untrue by the researches of Meissner[2] and of Voit,[3] who proved conclusively that the whole of the creatin and creatinin taken into the body is excreted unchanged in the urine twenty-four hours after its absorption. A material which is neither oxidized nor decomposed cannot form a source of energy, apart from the fact that the quantity of creatin and creatinin in bouillon is so small that it could not possibly be regarded as the source of muscular energy.

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[1] For the chemical constitution and the physiological significance of these compounds, see Lecture XIX.

[2] G. Meissner, *Zeitschr. f. rat. Med.*, vol. xxiv. p. 97 : 1865 ; vol. xxvi. p. 225 : 1866 ; and vol. xxxi. p. 283 : 1868.

[3] C. Voit, *Zeitschr. f. Biolog.*, vol. iv. p. 111 : 1868.

It has further been asserted that the addition of extract of meat increases the nutritive value of vegetable food, and gives the latter the same value as fresh meat. This assertion has also been refuted by Voit and his pupils,[1] who have shown by experiments made on man and on animals, that the unfavorable conditions of assimilation which characterize vegetable food are not improved by the addition of extract of meat.

Finally, the attempt has been made to attach a value as a food to extract of meat, in consequence of the considerable quantity of salts, "nutritive salts," which it contains. But, as I have already explained, there is no lack of salts in our food, but always an excess. Even for the growing organism there is only one inorganic constituent which could be deficient, *i. e.*, lime. But there is very little lime in meat-extract; the ash contains only 0.23 per cent. CaO.[2] No one would be likely to eat more than 30 grms. of meat-extract, which represents the amount obtained from 1 kgrm. of meat, and contains only 0.015 grm. of lime—that is, the same quantity as is contained in 10 c.cms. of cow's milk.

We must therefore conclude that meat-extract can only be looked upon as a pleasant adjunct to food. It is asserted even at the present time that extract of meat acts in the same stimulating and refreshing manner as tea and coffee undoubtedly do; but up to this date no direct action of extract of meat on muscles or nerves has been proved. The only investigation in this direction is due to Kemmerich,[3] who lays stress on the large amount of potassium salts contained in extract of meat, and asserts, as the result of his experiments, that they exert, in small doses a stimulating, in large doses a depressing, effect on the action of the heart. He therefore warns against immoderate use of the extract of meat.

So far as the potassium salts are concerned, the following is really the case.[4] The stimulating action on the heart which Kemmerich observed was in no way due to the potassium salts, but simply to the fact that he used rabbits for his experiments. Being very timid animals, the injection of almost any indifferent substance, such as a solution of sugar or of common salt, may easily produce a decided increase in the rate of the

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[1] Ernst Bischoff, *Zeitschr. f. Biolog.*, vol. v. p. 454 : 1869; and C. Voit, *Zeitschr. f. Biolog.*, vol. iv. pp. 359, 360 : 1870.

[2] G. Bunge, Pflüger's *Arch.*, vol. iv. p. 238 : 1871.

[3] Kemmerich, Pflüger's *Arch.*, vol. ii. p. 49 : 1869.

[4] G. Bunge, Pflüger's *Arch.*, vol. iv. p. 235 : 1871 : and *Zeitschr. f. Biolog.*, vol. ix. p. 130 : 1873. Lehmann has recently confirmed my results (see *Arch. f. Hygiene*, vol. iii. p. 249 : 1885).

pulse. The mere passage of the stomach sound is sufficient to have this effect. By large numbers of experiments both on dogs and on the human subject, I have convinced myself that the introduction of potassium salts into the stomach is never followed by the slightest acceleration of the pulse.

The paralyzing influence on the heart, observed by Kemmerich, is due to his having used an amount of potash salts quite out of proportion to the weight of the rabbit. To give a rabbit of 1000 grms. body weight, 5 grms. of potash salts is the same as giving a man 300 grms. An additional factor in the case of a rabbit is that it is unable to vomit. It is impossible to produce any influence on the heart of the dog, since an excessive dose of potassium salts is promptly followed by vomiting. I have found by numerous experiments that the maximum dose (about 12 grms.), which can be taken without causing vomiting, is quite without influence on the action of the heart. In cases where poisoning has actually ensued as the result of overdoses of potassium salts, death has been due to a gastro-enteritis, and not to any effect upon the heart. Potassium salts have a local corrosive effect. The gastric mucous membrane of animals into whom salts of potassium have been injected, is always hyperemic, and sometimes covered with ecchymoses. If the potassium salts are given in a very concentrated form, especially in powder, gastritis, with a fatal result, may be produced.

In all animals paralysis of the heart follows rapidly, if the solution of potassium salts be injected directly into the blood. As the result of my own experience, I have convinced myself that when 0.1 grm. KCl is injected into a medium-sized dog, an almost immediate arrest of the heart follows. Subcutaneous injection of potassium salts also causes cessation of the cardiac beat. But paralysis of the heart is never preceded by acceleration, but always by a slowing of the pulse.

It is hardly necessary to recur to experiment in order to show how entirely innocuous salts of potassium are when taken by the mouth; it has only to be borne in mind how large a quantity is constantly consumed with vegetable food. I have already noticed the fact that a man who lives chiefly on potatoes absorbs over 50 grms. of potash salts in the course of a day.

The potash salts, therefore, which occur in bouillon, cannot produce any effect on the heart, neither small doses stimulating it, nor large ones paralyzing it. But even if we could admit the exciting action of potassium salts, it would be difficult to see why we should take bouillon on account of the potash it contains, since we could get much more with almost any other form of food. Five grammes of extract of meat will make a plateful of bouillon, and they only contain 0.5 grm. potassium, the same quantity as in a small potato.

We see then that the only experiment which has been hitherto attempted to demonstrate the stimulating influence of extract of meat has not been successful.

It has frequently been asserted that the organic constituents of meat-extract exert an influence on the muscular nervous system, but never on sufficient ground. As regards creatin and creatinin in particular, Voit[1] has given details; he found that 6.3 grms. creatin and 8.6 grms. creatinin given to a dog produced no symptoms whatever. More recently Kobert[2] has endeavored to demonstrate an action of creatin on muscle. The experiments were conducted on frogs, and excessive doses of creatin used; but the result was ambiguous. Human muscle could hardly be influenced by the minute quantity (about 0.2 grm.) of creatin contained in an ordinary plateful of soup. This can be deduced *à priori*, quite apart from the observations of Voit. Our muscles contain about 3 per 1000 creatin.[3] The whole muscular system of an adult man, which amounts to about 30 kgrms., contains consequently about 90 grms. It is also found in the nervous system and in the blood. With regard to the small quantity of creatin which is taken in bouillon, absorbed, and at the same time rapidly excreted by the kidneys, we are uncertain whether it ever reaches the muscles at all. And even if a small quantity should do so, it can hardly be of any importance, when we know that the muscles already contain 90 grms. of creatin.

That some other organic constituent of meat-extract may produce an effect on the muscular or nervous system, must be admitted to be remotely possible; at present it is in no way proved. We know, with regard to bouillon, absolutely no more than that it tastes and smells agreeably. This fact, however, suffices to explain all the 'enlivening' and 'strengthening' virtues which common experience attributes to extract of meat and bouillon, and to recommend them as valuable and pleasant accessories of our food.

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[1] C. Voit, "Ueber die Entwicklung der Lehre von der Quelle der Muskelkraft," p. 39 : 1870; or *Zeitschr. f. Biolog.*, vol. vi. p. 343 : 1870.

[2] *Arch. f. exper. Path. u. Pharm.*, vol. xv. p. 56 : 1882.

[3] Fr. Hofmann, *Zeitschr. f. Biolog.*, vol. iv. p. 82 : 1868; M. Perls, *Deutsch. Arch. f. klin. Med.*, vol. vi. p. 243 : 1869.

LECTURE X

SALIVA AND GASTRIC JUICE

We have in previous chapters become acquainted with the various food-stuffs, and we must now trace their course through our bodies, and the gradual changes which they undergo.

The first fluid with which the food comes in contact on being introduced into the alimentary canal, is the SALIVA,[1] which is well known to be the secretion of three larger pairs of glands, and of the small glands in the mucous membrane of the mouth. The amount of saliva formed in the course of twenty-four hours is very considerable, and according to an approximate estimate of Bidder and Schmidt,[2] is about 1500 c.cms. This secretion might therefore be expected to play an important part in the processes of digestion, but it has not yet been found that it does so. The saliva has no effect on most articles of diet; starch alone is converted by its means into dextrin and sugar. But even this action is very inconsiderable; it is nothing compared with the powerful action of the pancreatic juice in breaking up starch. The period during which the saliva acts is of very short duration. The salivary ferment can only operate fully on starch under the faintly alkaline reaction which belongs to normal saliva. This action is immediately enfeebled or entirely neutralized by the acid gastric juice.[3] Thus only a very small portion of the starch consumed is split up by the salivary ferment. But the saliva

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[1] The processes of secretion in the salivary glands have been more closely investigated by Bernard, Ludwig, and Heidenhain than those in any other glands, and the results of these investigations are among the most important achievements of modern physiology. But these works have thrown no light upon the chemical processes in glandular activity. I therefore think it better to pass them over, especially as they are adequately described in all text-books of physiology.

[2] Bidder and Schmidt, "Die Verdauungssäfte und der Stoffwechsel," p. 14: Mitau and Leipzig, 1852.

[3] O. Hammarsten, Panum's Report in the *Jahresbericht über die Leistungen der ges Medicin.*, Jahrg. vi. vol. i.: 1871. [Cannon has shown however that at least half an hour may elapse before the food taken in with the meal is thoroughly mixed with the gastric juice. During this time the food remains in the fundus of the stomach, and in its inner portions salivary digestion can go on unchecked. (*Amer. Journ. of Physiol.*, vol. i. p. 359: 1898.)]

of some mammals has not even this slight action, as in the case of the carnivora, where for teleological reasons it might be expected to be absent.

As saliva is very abundantly secreted by carnivora, it is apparent that the decomposition of starch is not its main function.

It was hoped that by extirpating the salivary glands of dogs,[1] and then observing what disturbances took place in consequence, a conclusion might be arrived at as to the significance of saliva. No prejudicial effects were detected, although it was remarked that the dogs drank more water than usual with their accustomed and carefully regulated diet.

It appears that the saliva is chiefly of importance from a mechanical point of view. It moistens the food in the mouth and prepares it for the act of swallowing. At the same time the mouth is kept clean by the constant secretion. If particles of food were allowed to remain in the mouth, the acids which would be formed as the result of their decomposition, would injure the teeth; this is prevented by the mouth being continually kept moist with the alkaline saliva. If this view of the use of saliva is correct, we should expect the salivary glands of mammals living in water to be absent, since the food they take is always sufficiently moist, and the cavity of the mouth is constantly being washed out by water. This is in fact the case. The Cetacea lack salivary glands entirely, and in the Pinnipedia they are only rudimentary.

In the stomach the food meets with a second secretion, the GASTRIC JUICE, distinguished from all the other digestive fluids by its acid reaction. This acid reaction is due to the free hydrochloric acid. The proof of this was furnished by Carl Schmidt.[2] He determined the exact quantity of the chlorin and of all the bases, potash, soda, lime, magnesia, oxid of iron, and ammonia. The result was that, after allowing enough hydrochloric acid to saturate all the bases, a quantity remained over which amounted to about 2.5 to 4 grms. in 1 liter. Carl Schmidt determined, in addition, the amount of free acid by means of titration, and obtained almost exactly the same numbers as in the case of the determination by weight.

If we now inquire into the significance of this free acid, we find that most writers regard it as subserving the digestion of proteids. Proteids, and gelatins, which are closely allied to

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[1] C. Fehr, "Ueber die Exstirpation sämmtlicher Speicheldrüsen beim Hunde," Dissert.: Giessen, 1862.

[2] Bidder and Schmidt, "Die Verdauungssäfte und der Stoffwechsel," pp. 44, 45: Mitau and Leipzig, 1852.

them, are in fact the only food-stuffs which are altered by the gastric juice. They are changed into peptones,[1] which are distinguished from proteids and gelatins by the fact that they no longer retain their colloid properties, are no longer coagulable, are more readily diffusible through animal membranes, and consequently appear particularly suited for absorption into the blood. This peptonizing action is attributed to a ferment called pepsin.[2] Pepsin is however only effectual in the presence of a free acid. Hence up to the present time it has been the custom to regard free acid as being only of use in rendering the action of pepsin possible.

But we cannot be content with this explanation ; we know that the pancreatic ferment acts even more energetically than the gastric juice, and that it is most efficacious when the reaction is faintly alkaline. Why should the gastric glands have the severe labor of separating free hydrochloric acid from the alkaline blood, if the organism can effect its purpose by much simpler means—by the secretion of an alkaline fluid? The free acid must have some other significance. At the present day, when our knowledge of putrid fermentation and the means of combating it has so much increased, and when we have found that free mineral acids are to be counted among the most effectual antiseptics, it is not unreasonable to attribute this function to the free hydrochloric acid of the gastric juice. It has the duty of killing the microörganisms which reach the stomach with the food. These would otherwise set up processes of decomposition in the alimentary canal, and thus destroy a part of the food before its absorption, whilst the products of decomposition would produce disagreeable symptoms, or even, as a cause of disease, endanger life.

N. Sieber,[3] in Nencki's laboratory in Berne, determined the strength of the hydrochloric acid which suffices to prevent the development of putrefactive organisms in substances capable of putrefaction, and arrived at the following results.

If 50 grms. finely chopped meat were put into an open flask with 300 c.cms. of a 0.1 per cent. solution of hydrochloric acid, only a scanty development of micrococci and bacilli took place in twenty-four hours. After forty-eight hours they had some-

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[1] The nature and significance of peptones will be discussed later on (see Lectures XI. and XIII.).

[2] See Lecture X. for the experiments on the isolation of pepsin. Besides pepsin, another ferment, the 'rennet ferment,' is included in the gastric juice, and this causes the coagulation of milk in the stomach. Nothing is known concerning the physiological import of this coagulation. I therefore omit all account here.

[3] N. Sieber, *Journ. f. prakt. Chem.*, vol. xix. p. 433 : 1879.

what increased, and on the third day the fluid presented a distinctly putrefactive odor, and a weakly acid reaction.

When the experiment was made, *ceteris paribus*, with 0.25 per cent. hydrochloric acid, isolated non-motile organisms were not found till the seventh day, and pronounced formation of mould not until the ninth day.

In a third experiment carried out, *ceteris paribus*, with 0.5 per cent. HCl, "no trace of putrefaction" appeared until the seventh day.

Miquel[1] attained the same result, finding that from 0.2 to 0.3 grm. mineral acid was sufficient to render 100 c.cms. of bouillon incapable of undergoing putrefaction.

In the gastric juice of a dog—obtained from a gastric fistula, and from which all admixture with saliva had been prevented by previous ligature of all the salivary ducts—C. Schmidt[2] found in eight analyses, from 0.25 to 0.42 per cent. HCl, the mean of the eight analyses being 0.33 per cent. Heidenhain[3] found in the secretion of the glands of the cardiac end of the stomach,[4] by means of titration in thirty-six cases, from 0.46 to 0.58, as a mean 0.52 HCl per cent.

In Hoppe-Seyler's laboratory,[5] the free acid contained in the undiluted gastric juice, obtained from a man by the aid of the stomach-pump, was determined; 0.3 per cent. HCl was found.

We thus arrive at the striking result that the quantity of free hydrochloric acid in the gastric juice exactly corresponds to the quantity which is necessary to prevent the development of putrefactive organisms. This coincidence cannot be accidental.

It might be objected to this that the gastric juice is diluted by the saliva and the food. On the other hand it must be remembered that, owing to the constant peristaltic action of the stomach, different portions of its contents are constantly being brought into contact with the secreting wall, and consequently into contact with hydrochloric acid of the strength requisite to kill bacilli. In fact, under normal conditions, pronounced putrefactive decomposition never occurs in the stomach. But if, under pathological conditions, the secretion should be interfered with, the processes of fermentation and decomposition may reach a very high degree.

The antiseptic action of the gastric juice was noticed more

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[1] Miquel, *Centralbl. f. allgem. Gesundheitspflege*, vol. ii. p. 403: 1884.

[2] Bidder and Schmidt, *loc. cit.*, p. 61.

[3] Heidenhain, Pflüger's *Arch.*, vol. xix. p. 153: 1879.

[4] The method of obtaining the secretion from these glands will be discussed later on.

[5] Dionys Szabó, *Zeitschr. f. physiol. Chem.*, vol. i. p. 155: 1877.

than a hundred years ago by Spallanzani.[1] He found that by moistening meat with gastric juice he could prevent decomposition for many days. But when, *ceteris paribus*, water was used instead of gastric juice, an unbearable putrid odor was speedily developed. A snake had swallowed a lizard. After sixteen days Spallanzani opened the stomach ; the lizard was half digested, but gave no odor of decomposition. Spallanzani even observed that the gastric juice not only prevented decomposition, but stopped putrefaction which had already begun. He found that when decomposing meat was introduced into the stomachs of various animals, it lost its putrefactive character after a time, and particularly its putrid odor.

A strong point in favor of the view that the antiseptic action of the gastric juice constitutes its chief importance is found in the fact that, in a whole series of the lower animals, the commencement of the alimentary canal secretes a fluid very rich in mineral acid, but containing no ferment, and having no special action on the food. This important fact was first noticed by the zoölogist Troschel.[2] He was making a scientific journey with his teacher, Johannes Müller, and whilst in Messina he examined a large species of mollusc, which is there found in the sea, the *Dolium galea.* It so happened that one of these creatures, whilst being examined, suddenly ejected from its mouth a stream of clear fluid, which fell on the floor. The latter was covered with marble, and the fluid at once caused a violent ebullition of carbonic acid. Troschel collected a large quantity of this secretion from a number of these molluscs. The weight of one of the molluscs amounted to from 1 to 2 kgrms., and the two large glands which pour the acid fluid into the mouth, and are hence designated salivary glands by zoölogists, weigh together from 80 to 150 grms. On grasping the proboscis of the animal by its trumpet-like enlarged end, the secretion is ejected, and can be collected in a vessel. The quantity was very small, but amounted in one case to fully 6 loth[3] Prussian weight. It was therefore easy to collect a quantity sufficient for investigation.

Troschel, on his return to Bonn, made over the whole of the secretion to the chemist Boedeker for analysis. It struck

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[1] Spallanzani, "Expériences sur la digestion," Trad. par Senebier, pp. 95, 97, 145, 320, 330, nouvelle édit.: Genève, 1784. This work is strongly to be recommended to young physiologists, as an example of impartial investigation, logical conclusions, indomitable scepticism, and the purest enjoyment of truth for its own sake. The same qualities are visible in all Spallanzani's other works.

[2] Troschel, Poggendorff's *Annal.*, vol. xciii. p. 614: 1854; or *Journ. f. prakt. Chem.*, vol. lxiii. p. 170: 1854.

[3] [A 'loth' is half an ounce.]

Boedeker at once that the fluid displayed no trace whatever of putrefaction or fermentation, or of mouldiness, and that it had no smell, although it had been kept for half a year in a stoppered bottle. The analysis yielded so large a quantity of sulphuric acid that, after saturation of all the bases present, potash, soda, magnesia, a little ammonia, and a trace of lime, there still remained 2.7 per cent. H_2SO_4. In addition, the secretion contained 0.4 per cent. of hydrochloric acid. These results of Troschel and Boedeker were confirmed by Panceri and De Luca.[1] They found in three analyses of the saliva of *Dolium galea*, 3.3, 3.4, 4.1 per cent. of free sulphuric acid. They also proved the presence of secretions containing free sulphuric acid in another species of mollusc.

In more recent times, the saliva of *Dolium galea* has been examined by Maly.[2] He has determined the sulphuric acid by titration, and found 0.8 and 0.9 per cent. H_2SO_4 in two determinations. The secretion had no digestive influence on any article of food. Proteid and starch remained totally unchanged.

Frédéricq[3] found that the salivary glands in the octopus had an acid reaction. The extract of these glands had no digestive influence.

We must now ask how this remarkable phenomenon, the secretion of the strongest free mineral acids from the alkaline tissues, is to be explained.

That the tissue of the gastric mucous membrane does as a matter of fact give an alkaline reaction, has been shown by Brücke[4] by the following experiment. He removed a strip of the muscular coat from a rabbit recently killed, and then with curved scissors cut out a piece of the parenchyma of the glands without quite touching the internal surface of the mucous membrane. The fragment thus obtained could be crushed between blue litmus paper without causing a red spot, whilst this was produced at once on contact with the internal surface.

The material for the formation of the hydrochloric acid in the gastric glands is undoubtedly yielded by the blood in the form of chlorid of sodium, which is the chief constituent of the ash of the blood-plasma and of lymph. But nevertheless carbonate of soda is contained in both blood and lymph, which have in consequence an alkaline reaction. How then is the

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[1] S. de Luca and P. Panceri, *Compt. rend.*, vol. lxv. pp. 577, 712: 1867.

[2] Maly, *Sitzungsber. d. k. Akad. d. Wissensch.* Math. nat. Classe, vol. lxxxi. part 2, p. 376: Wien, 1880.

[3] Frédéricq, *Bulletins de l'Acad. Roy. de Belgique*, ser. ii. vol. xlvi. No. 11: 1878.

[4] Brücke, *Sitzungsber. d. Wien. Akad.*, vol. xxxvii. p. 131: 1859.

hydrochloric acid set free from the sodium chlorid of the alkaline plasma? Two suppositions alone are possible. Either the hydrochloric acid is separated from the sodium by the aid of some kinetic energy, or the hydrochloric acid is driven from its base by another acid. With regard to the first possibility, we are only acquainted with one kind of kinetic energy which is able, outside the organism, to separate hydrochloric acid from an aqueous solution of chlorid of sodium, and that is the electric current. There was a period in the development of physiology when a tendency existed to ascribe anything which could not be understood to electricity. It was then thought that the appearance of free hydrochloric acid in the gastric juice could be explained by the supposition of electrical currents in the gastric glands. But at the present day this view is hardly entertained; neither are there any valid grounds for its adoption.

With regard to the second supposition, the displacement of the hydrochloric acid by another acid, there was till recently a prejudice against it, since it was thought that an acid could only be displaced by a stronger acid. The question is whether this opinion is well founded, and what we mean by the terms weaker and stronger acid. The most plausible definition is obviously the following: of two acids, the one which requires a greater expenditure of energy to separate it from the same base, and which, on reuniting, produces more energy, is the stronger. In this sense, as proved by calorimetric experiments, sulphuric acid is stronger than hydrochloric acid, hydrochloric acid than lactic acid, and the latter than carbonic acid. But it is erroneous to suppose that the weaker acid is never able to drive out the stronger. From the researches of Jul. Thomsen,[1] we know with certainty that every acid drives out a portion of every other acid from its union with a base. It may even happen that the weaker acid unites with the bulk of the bases present. If hydrochloric acid be added to a solution of sulphate of soda, heat is absorbed, and the temperature of the solution falls; more heat is used up in the separation of the soda from the sulphuric acid than is produced by its union with hydrochloric acid. With the aid of the calorimeter, it is possible to follow these experiments quantitatively with exactness. From the known amount of heat produced by the union of hydrochloric acid and sulphuric acid with sodium, and from the diminution of temperature observed when hydrochloric acid acts on a solution of sulphate of sodium, it can be exactly calcu-

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[1] Jul. Thomsen, "Thermochemische Untersuchungen," Poggendorff's *Annal.*, vols. cxxxviii.–cxliii.: 1869–1871.

lated how much sulphuric acid is displaced by the hydrochloric acid. Thomsen found that when equivalent quantities of hydrochloric acid and sulphate of soda react upon one another, the hydrochloric acid combines with two-thirds of the sodium present, leaving only one-third to the sulphuric acid. The weaker acid takes up twice as much as the stronger. Strength, as defined above, is therefore not the determining factor. We are compelled to form a new idea of the different strengths of chemical affinity, and Thomsen has introduced the term "avidity" to express this idea. The avidity of hydrochloric acid is therefore twice as great as that of sulphuric acid.

Thomsen found the avidity of organic acids to be much less. The avidity of oxalic acid is four times less than that of hydrochloric acid; that of tartaric acid twenty times, that of acetic acid thirty-three times, less. If therefore equivalent quantities of acetic acid, hydrochloric acid, and soda react upon one another in an aqueous solution, the acetic acid takes $\frac{1}{34}$ of the total soda; the hydrochloric $\frac{33}{34}$. If, however, more than one equivalent of acetic acid react upon one equivalent of hydrochloric acid and one equivalent of sodium, more than $\frac{1}{34}$ of the sodium unites with the acetic acid, and the further increase will be in proportion to the greater amount of acetic acid present. This phenomenon is known by the name of the "influence of mass." By the influence of mass, acids of the weakest avidity are able to unite with the bases and to displace acids of the greatest avidity. No acid has an avidity = 0. Even carbonic acid, feeble as it is, must be able, by the influence of mass, to displace a part of the strongest acid.

Finally, we must suppose that even the weakest acid, water, may displace a part of the strongest from their salts. If we dissolve neutral chlorid of sodium in water, there will be, in addition to the chlorid of sodium, a small trace of HCl and NaOH contained in the solution. In the case of certain metallic salts, which form basic salts, soluble with difficulty, the action of water in displacing the strongest mineral acids can be easily demonstrated. If we dilute a solution of nitrate of bismuth with water, the basic salt is precipitated, and we find free nitric acid in solution. In this case the mass-influence of the feeble acid is aided by the affinity of the strong acid for water.

The displacement of strong mineral acids by weak organic acids may be shown in other ways than the thermo-chemical. Maly[1] introduced into the lower portion of a tall cylinder

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[1] Maly, Liebig's *Annal.*, vol. clxxiii. pp. 250–257: 1874.

a solution of common salt and lactic acid, and carefully poured water upon it. After a considerable time the upper stratum was removed and analyzed. It was found to contain more chlorin than was sufficient to saturate the sodium that was present. It follows that free hydrochloric acid had diffused into the water.

If we take these facts into consideration, there is nothing peculiar in the separation of free hydrochloric acid from alkaline blood. We know that the blood always contains free carbonic acid which, by the influence of mass, has the power of setting free a small amount of hydrochloric acid from the chlorid of sodium. The amount may be almost imperceptible, but as soon as this small quantity of free hydrochloric acid, which corresponds to the free carbonic acid, diffuses away, the carbonic acid, by its mass-influence, must again set free another small amount of hydrochloric acid, and so on.

There is thus nothing extraordinary in the occurrence of free hydrochloric acid. But what is enigmatical is the power epithelial cells possess of directing the hydrochloric acid, liberated from the chlorid of sodium, always in the one direction towards the excretory duct of the gastric glands, and the carbonate of sodium, formed from the carbonic acid, always in the opposite direction, back towards the lymph and blood-vessels. But this enigma confronts us everywhere in living tissue. Each cell has the power of attracting or rejecting different materials, according to the object they are destined to fulfil, and of forwarding them in different directions.[1] It is therefore no fresh problem that confronts us in the attempt to explain the occurrence of free hydrochloric acid in the gastric glands, and, in fact, "every explanation of the phenomena of nature consists in referring an apparently fresh difficulty back to old and well-known problems."

The mass-action of carbonic acid appears also to liberate the mineral acids in the salivary glands of *Dolium galea*. De Luca and Panceri observed that a strong current of gas-bubbles arose from the glands when they were cut up and immersed in water. The gas, being completely absorbed by potash, was therefore pure carbonic acid. A gland weighing 75 grms. produced, when covered with water, 200 c.cms. of carbonic acid, or nearly three times its volume. It must likewise be remembered that the surrounding fluid retained a considerable quantity of carbonic acid, and that the gland itself remained saturated with carbonic acid. Thus at least four times its volume of carbonic acid was absorbed in the gland.

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[1] Compare above, p. 4, and below p. 147, and Lecture XXI.

As water at an ordinary temperature absorbs from an atmosphere of pure carbonic acid its equal volume of carbonic acid, we must conclude that the carbonic acid in the glands was under more than fourfold atmospheric pressure; or we must assume that the carbonic acid was in part loosely combined. An exact estimate of the tension of carbonic acid which would prevent the escape of the gas from the gland, would help to decide this question.

It is quite possible that much carbonic acid is also liberated in the epithelial cells of the gastric glands, either by a fermentative process or by the oxidation of organic compounds.

At the same time we are not obliged to ascribe the displacement of the strong mineral acids to the most feeble acid, carbonic acid. It is quite conceivable that, in the epithelial cells of the glands, organic acids may be liberated by the action of ferments from neutral organic compounds — for instance, lactic acid from neutral sugar, which is invariably a constituent of blood-plasma and of lymph. It is even possible that the strongest mineral acid, sulphuric acid, may be liberated by a fermentative action directly from a neutral compound of sulphur, as, for instance, from proteid. That this is possible may be seen from an example in organic chemistry—I mean the decomposition of a glucoside, myronic acid. The potassium salt of myronic acid, a neutral compound, splits up by the action of a ferment into sugar, oil of mustard, and bisulphate of potash, which latter, Graham[1] has shown, at once decomposes in an aqueous solution into free sulphuric acid and neutral sulphate of potash. Besides this, free sulphuric acid might also be liberated by oxidation from neutral organic sulphur compounds.

At present we do not know by which, of all these conceivable processes, the strong mineral acids are liberated in glandular tissue. I have called attention to these possibilities so as not to be obliged to have recourse to electricity for an explanation.

The secretion of the free hydrochloric acid does not occur in all glands of the gastric mucous membrane. The mucous membrane in the region of the pylorus which, even with the naked eye, can be distinguished by its pale color from the rest of the membrane, yields an alkaline secretion which only

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[1] Graham, Liebig's *Annal.*, vol. lxxvii. p. 80: 1881. In a diffusion experiment with bisulphate of potassium, more sulphuric acid diffused than corresponded to the acid salt, and a little neutral sulphate of potassium crystallized out in the diffusion-cell.

contains pepsin. The glands of the rest of the membrane yield an acid secretion which contains pepsin as well as free acid. This was shown to be the case by Klemensiewicz[1] and Heidenhain[2] by the following method :—

By an incision in the linea alba of a dog that has been fasting from thirty-six to forty-eight hours, the stomach is drawn out by two parallel incisions, avoiding the large blood-vessels, the pyloric zone is cut out, the two edges of the resected stomach are sewn together, and the organ thus reduced in size is replaced. Then the excised pylorus is sewn together at one end to form a sac, while the other end is sewn into the abdominal wound. By the careful use of antiseptics in the treatment of the wounds, and by abstinence from food during the following days, the animals are kept alive after this severe operation. Heidenhain was able to observe one of the dogs, that he had experimented upon, for ten weeks. The slimy clear fluid secreted in the isolated pylorus invariably gave an alkaline reaction, and, on the addition of 0.1 per cent. of hydrochloric acid, produced a peptonizing action on proteid. As dilute hydrochloric acid by itself cannot convert proteid into peptone at the temperature of the body, we must assume that the pyloric secretion contains a ferment.

In a similar method to that adopted for the pylorus, Heidenhain isolated a rhombic portion of the fundus of the stomach, converted it into a sac, and attached the open end to the abdominal wound. A dog thus operated upon was kept under observation for five weeks. The secretion collected from the abdominal wound always possessed an acid reaction, and manifested a pronounced peptonizing influence, showing that it also contained pepsin.

Still further progress has been made in determining exactly where the hydrochloric acid arises, and special cells of the gastric glands, the so-called border or oxyntic cells, are regarded as its place of origin. The reasons which are adduced in favor of this conclusion are by no means convincing; but it would lead me too far to consider the whole question in detail.[3]

Since it is possible to keep an animal alive after resection of the pylorus, the question occurs as to whether the whole

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[1] Rudolf Klemensiewicz, *Sitzungsberichte der Wiener Akad.*, Math. nat. Classe, vol. lxxi. part iii. p. 249: 1875.

[2] Heidenhain, Pflüger's *Arch.*, vol. xviii. p. 169: 1878; and vol. xix. p. 148: 1879.

[3] An account of the literature on this question is given in the chapter, "Physiologie der Absonderungsvorgänge," by Heidenhain, in Hermann's "Handbuch der Physiologie," vol. v. part i.: Leipzig, 1883.

stomach might not be removed without destroying life. Such an operation would be likely to give us much information concerning the true importance of the stomach.

Czerny, the eminent surgeon, and his assistants, Kaiser and Scriba, carried out this operation on dogs. In the year 1878, Kaiser[1] published the result of the operations, and communicated the facts that, of the dogs in which the stomach had been almost completely removed, one had survived three weeks, another—operated on December 22, 1876—was still living. At first the animals were fed only on very small quantities of milk and minced meat, as otherwise vomiting ensued. The second dog, after a two-months' interval, required no further care, and ate ordinary food like the other dogs. The weight of the dog before the operation was 5850 grms.; after the operation it fell to 4490 grms. by January 22, but then increased again till it amounted to 7000 grms. on September 10.

In Leipzig, in the year 1882, Ludwig and his pupil Ogata[2] were engaged in investigating the functions of the stomach. It occurred to them that it would be interesting to learn what had become of Czerny's dogs. Ludwig wrote to Czerny at Heidelberg, who answered by sending the dog in a perfectly healthy state to Leipzig. It was in excellent spirits, and ate all kinds of food with a keen appetite. The feces were normal. In consequence of the abundant food it put on weight, and it did not appear to differ in any way from an ordinary dog. With Czerny's consent, the dog was killed in the spring of 1882. "The post-mortem showed that only a very small portion of the cardiac end of the stomach remained, and this was dilated into a small cavity filled with food." The dog had therefore lived for more than five years without a stomach.

Ludwig and Ogata[3] adopted another way of excluding the stomach from participation in the functions of digestion, and of observing what variations from the normal course of events were then produced. They introduced the food directly into the duodenum, by means of a fistula which had been established close to the pylorus, and then closed the pylorus by means of a gutta-percha ball provided with a long tube which projected from the fistula, and by means of which the ball could be so

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[1] F. F. Kaiser, in Czerny's "Beiträge zur operativen Chirurgie," p. 141: 1878. These results have been confirmed by F. de Filippi, *Deutsch. med. Wochenschr.*, p. 780: 1894; J. Carvallo and V. Pachon, "Arch. de Physiol.," vol. xxvii. pp. 349 and 766: 1896, and U. Monari, *Beitr. z. klin. Chir.*, vol. xvi. p. 479: 1896.

[2] M. Ogata, Du Bois' *Arch.*, p. 89: 1883.

[3] M. Ogata, *loc. cit.*, p. 91.

filled with water that the passage from the stomach to the duodenum was completely cut off.

In this way it was possible to introduce at one time very large quantities of food, such as pounded egg and minced meat, into the duodenum without causing any disturbance. Two injections per diem were sufficient to maintain the animal's weight. The food was almost completely used up, and the feces exhibited normal characters, such as are observed in feeding by the mouth. The only exception was that sometimes the connective tissue of the food was not quite so completely absorbed as is normally the case. It was however not a matter of indifference whether the food was previously cooked or not. For instance, minced meat was completely absorbed only if given raw. If administered after it had been boiled, it was ejected *per anum* a few hours later but little or entirely unaltered. Minced pork behaved in an opposite way, and was more completely digested after having been lightly boiled than when given raw.

Ludwig and Ogata conclude from their observations that "the stomach is not absolutely necessary to satisfy the requirements of digestion, either as a reservoir of food or to produce the gastric juice."

No experiment was made in which a dog, after removal of the stomach, was fed by the direct introduction into the intestine of putrid meat, a diet which agrees very well with normal dogs. The chief function of the stomach would at once have been evident had this been done.

Encouraged by the success of these experiments on animals surgeons have carried out, with more or less success, the extirpation of the stomach in man, especially in cases of cancer of the stomach. It is advisable, when possible, to leave a portion of the stomach, however small it may be, since this portion will afterwards increase in size, and thus take on the chief function of the stomach, *viz.*, as a reservoir and protective organ for the intestine. In 1895 Professor Schuchardt, in Stettin, excised the whole stomach of a patient with the exception of a small portion (about three fingers' breadth) of the cardiac end. This patient lived two and a half years after the operation, and was during this time perfectly well. At the autopsy a stomach was found with a capacity of 500 cc. It was on this account that the patient, who at first could take only a small portion of food at a time, was later on able to take his meals like any other person.[1]

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[1] Communicated by C. Schlatter in the *Correspondenzbl. f. schweizer Aerzte*, vol. xxvii. p. 705: 1897. Here also several other instances of almost complete extirpation of the stomach are recorded.

At the Congress of Swiss Physicians in Olten on October 30, 1897, the surgeon, C. Schlatter, of Zurich,[1] showed a woman in whom he had *completely* extirpated the stomach, on account of a hard tumor involving the whole stomach from pylorus to cardia. The esophagus was too far off from the duodenum to allow of the two being sewn together. The esophagus was therefore made to open into a loop of the small intestine, and the upper end of the duodenum was closed by sutures. The bile and pancreatic juice thus poured themselves into a blind portion of the gut, by which they were conducted to the small intestine, where the food entered it through the esophagus. The patient who had undergone this operation had already survived it eight weeks when she was shown at the Meeting, and in this time had put on 4.4 kilos. in weight. Of course the patient could take only small quantities of fluid or of finely minced food at a time.

The antiseptic powers of the gastric juice have, like most things, a limit. Certain bacteria and among them pathogenic organisms exhibit, especially in their spore stage, such a resistance to chemical agents that the hydrochloric acid of the stomach does not kill them. Thus Falk[2] observed that the tubercle bacillus was not acted upon by gastric juice. Anthrax virus, taken from the spleen of animals which had died of splenic fever, was rendered inert both by gastric juice and by a 0.11 per cent. solution of hydrochloric acid. The spores of anthrax bacilli were as a rule not affected by dilute hydrochloric acid or gastric juice, though they were in a few cases. These statements have been fully confirmed by Frank.[3]

The comma bacillus, which is said to cause cholera, is very easily killed by dilute hydrochloric acid. In consequence, it is not possible to infect animals by administration of the comma bacillus by the mouth. But it is possible sometimes to excite attacks resembling cholera, by injecting pure cultivations of this bacillus into the small intestine or into the stomach, after previously washing out the organ with a solution of carbonate of soda.[4] The bacteria which produce lactic and butyric fermentations appear to be more resistant to hydrochloric acid; at any rate, they are found very frequently, probably always, in the human intestine,[5] and after eating carbohydrates, a small

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[1] *loc. cit.*

[2] Falk, Virchow's *Arch.*, vol. xciii. p. 117: 1883.

[3] Frank, *Deutsche med. Wochensch.*, No. 24: 1884. Compare also H. Hamburger, "Ueber d. Wirkung des Magensates auf pathogene Bacterien," Dissert.: Breslau, 1890. A complete account of the literature is here given.

[4] Nicati et Rietsch, *Rev. Scien.*, p. 658: 1884; R. Koch, *Deutsch. med. Wochensch.*, No. 45: 1884.

[5] H. Nothnagel, *Centralbl. f. d. med. Wissensch.*, No. 2: 1881.

amount of lactic and butyric acids is probably always found in the stomach. It has often been asserted that this decomposition is produced by unorganized ferments, but it has never been strictly proved.[1] In the normal feces of man, other species of bacteria are constantly found.[2]

Recently, Nencki and his pupils[3] have investigated the microörganisms occurring in the intestinal contents obtained from a fecal fistula affecting the lower end of the small intestine of a patient. On meat diet they found six different kinds of bacteria, one kind of yeast, and one mould. On vegetable diet (peas) there were also yeasts, but no mould. There were also six kinds of bacteria, of which only one was identical with those found on a meat diet. These microörganisms were grown in pure cultures in order to determine what part each species played in the processes of decomposition occurring in the intestine.

In pathological conditions, as in so-called catarrh of the stomach, when the secretion of free hydrochloric acid is suppressed, and the amount of alkaline mucus yielded by the surface of the stomach is increased, the reaction may indeed become alkaline, and then all sorts of bacteria are able to grow luxuriantly.[4] Lactic and butyric acids especially are formed in abundance. The presence of acetic acid has also been demonstrated; this is probably produced from the alcohol, owing to the oxidizing influence of the air which has been swallowed. Alcohol arises by fermentation from the carbohydrates. Not only does yeast, which has actually been observed in the stomach, produce alcohol, but certain varieties of bacteria appear also to do so.[5]

The gases which are formed by the processes of fermentation in the stomach are carbonic acid gas, hydrogen, and marsh gas.[6] Under pathological conditions they may be formed in considerable quantities, and so cause dilatation of the organ. In one case of dilatation of the stomach Fr. Kuhn[7] found that one

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[1] See Ferd. Hueppe, *Mittheil. a. d. kaiserl. Gesundheitsamte.*, vol. ii. p. 309: Berlin, 1884. Nencki u. Sieber, *Journ. f. prakt. Chem.*, vol. xxvi. p. 40: 1882.

[2] See Berthold Bienstock, *Zeitschr. f. klin. Med.*, vol. viii. p. 1: 1884; L. Brieger, *Zeitschr. f. physiol. Chem.*, vol. viii. p. 306: 1884.

[3] Macfadyen, Nencki, and Sieber, *Arch. f. exper. Path. u. Pharm.*, vol. xxviii. p. 325: 1891.

[4] An account of the microörganisms which occur in the stomach under pathological conditions, as well as the literature of the subject will be found in the paper by W. de Bary, "Beitr. zur Kenntniss der niederen Organismen im Mageninhalte" (*Arch. f. exp. Path.*, vol. xx. p. 243: 1885).

[5] L. Brieger, *Zeitschr. f. physiol. Chem.*, vol. viii. p. 308: 1884.

[6] G. Hoppe-Seyler, *Deutsch. Arch. f. klin. Med.*, vol. l. p. 82: 1892.

[7] Fr. Kuhn, *Zeitschr. f. klin. Med.*, vol. xxi. p. 584: 1892.

liter of gastric contents developed four liters of gas in four hours when kept outside the body at the body temperature. This gas had the following composition :—

CO_2	20.0 per cent.
O	8.3 "
H	30.9 "
CH_4	0.3 "
N	40.5 "
CO	A trace

At times sulphuretted hydrogen may also be formed in the stomach contents.[1]

If the organic acids reach the esophagus, they cause heart-burn by the irritation of the mucous membranes of the esophagus and fauces. This symptom is usually treated with carbonate of soda or magnesia, without considering that the cause of the disorder is thereby increased rather than diminished. The free acids are neutralized by the drug, and the growth of the fungi and fermentation proceed more rapidly. The only proper treatment of heart-burn would be to recommend abstinence to the patient, until the stomach was empty and disinfected by its normal hydrochloric acid.

The contents of the stomach in a considerable number of diseases have recently been examined by means of the stomach-pump.[2] It has been found that the free hydrochloric acid is frequently absent in the gastric juice of the patients, whilst pepsin is always present.[3] For this reason, dilute hydrochloric acid is frequently prescribed as a remedy in dyspepsia. Many practitioners assert that they have obtained a favorable result with it. I would however warn against a too energetic treatment with free hydrochloric acid, especially a very prolonged use in chronic gastric trouble. Hydrochloric acid is partly excreted in a free state by the kidneys. We are

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[1] J. Boas, *Deutsch. med. Wochenschr.*, No. 49, p. 1110: 1892.

[2] O. Minkowski, *Mittheilungen aus der med. Klinik zu Königsberg i. Pr.*, p. 148: 1888. The earlier literature is discussed here.

[3] It has frequently been asserted that free hydrochloric acid is partly or completely replaced by lactic acid, even in the normal gastric juice, but especially in certain diseases. It has even been asserted that the absence of free hydrochloric acid might serve for diagnostic purposes, its absence having been regarded as indicative of carcinoma of the pylorus. A whole series of convenient reactions for the demonstration of free hydrochloric acid have also been devised. But these tests have not proved reliable, nor has the absence of free hydrochloric acid as a sign of a definite malady been found to be trustworthy. Just as little has the presence of lactic acid as a constituent of normal gastric juice been proved. It would appear that the lactic acid found in the stomach never comes from the gastric glands, but always from the carbohydrates of the food. An account of the extensive literature on this subject will be found in *Deutsch. Arch. f. klin. Med.*, vol. xxxix. p. 233: 1886, by J. von Mering and A. Cahn, entitled "Die Säuren des gesunden und kranken Magens."

ignorant whether we should not be throwing too much work upon these organs, and whether we should not injure their tissue by a too prolonged use of it. We are also unaware what other tissues are affected by the hydrochloric acid on its way from the stomach to the kidney, and what variations from their normal chemical processes it causes. A diminution of their alkalescence can never be a matter of indifference, since the intensity of the processes of oxidation and disintegration must be intimately bound up with the reaction of the tissue, judging at any rate from analogous chemical processes that we are familiar with outside the body. So long as we are ignorant on these points, we must be cautious in the use of powerful remedies like free mineral acids. In most cases, the best advice would perhaps be that of abstinence, until the whole lining of the stomach has become disinfected by normal undiluted gastric juice. Even in weakened and anemic individuals abstinence is perhaps more effectual than hydrochloric acid and pepsin, accompanied by more food than their instinct tells them they can dispose of. The administration of preparations of pepsin and pancreatin is a useless measure.

It should also be noted that to begin a meal with soup, and to drink much during a meal, are not rational proceedings; because the gastric juice becomes too much diluted, and loses its disinfectant properties. There is an ancient and good dietetic rule, not to drink for an hour or two after eating, when thirst is actually felt. It is noticeable that to the healthy instinct of children soup is repugnant. At periods when cholera is prevalent, it is advisable to avoid all voluminous foods and to reduce liquids to a minimum, so that the whole contents of the stomach may be impregnated with hydrochloric acid of the necessary concentration.

The question as to why the stomach does not digest itself is one which has caused much discussion. The tissues of the stomach consist entirely of digestible matter—proteid and gelatin. In fact, as soon as life ceases, self-digestion of the stomach takes place. In post-mortem examinations, it is common to find a part of the mucous membrane of the stomach softened or dissolved, and this phenomenon is especially marked in the bodies of healthy and powerful individuals who have met with a sudden death in the midst of full digestion. The old doctrine, that the 'softening of the stomach' was a pathological process going on during life, is now definitely rejected.[1] The reason why the process of digestion does not proceed further in

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[1] Elsässer's "Die Magenerweichung der Saüglinge" (Stuttgart and Tübingen, 1846), should be read in this connection. The earlier literature is also critically

the dead body is due to the process of cooling down which takes place.

If a dog be killed during digestion and the body be kept warm, we find, after two or three hours, not only a self-digestion of the stomach, but also of the neighboring parts, liver and spleen. Why does this solution not take place in the living animal? This question was taken up by John Hunter,[1] who supposed that "the living principle" hindered self-digestion. Cl. Bernard[2] thought to refute this view by the following experiment. He placed the leg of a living frog into the gastric fistula of a living dog. The leg was soon digested, and the frog remained alive. The living principle had not therefore protected the frog. Pavy[3] introduced the ear of a live rabbit into the gastric fistula of a dog. A large part of the ear was digested in a few hours, the tip being entirely dissolved.

Pavy[4] thought that an explanation of the power of resistance possessed by the living gastric mucous membrane was to be found in the quantity of blood contained in it. He supposed that the constant rapid rush of alkaline blood and alkaline lymph through the tissues did not allow the pepsin, which can only peptonize in acid solution, to do its work. If the circulation were arrested, self-digestion began. Pavy showed that, after tying the blood-vessels of the stomach in dogs, a part of the mucous membrane was digested; in rabbits, even perforation of the stomach set in. He opened a dog's stomach and ligatured a portion of the opposite wall so that the piece that was tied hung into the stomach, and the piece was digested as if it had been swallowed. Pavy concludes from these experiments that the alkalies in the blood prevented self-digestion; and this interpretation has been commonly accepted. But the conclusion is not correct. The alkalies are not the only things carried to the epithelial cells by the blood.

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treated here. The most prominent pathological anatomists and medical men have adopted Elsässer's view, that the softening of the stomach is a post-mortem process. It is only in very rare and exceptional instances that softening and perforation of the stomach set in before death. See W. Mayer, "Gastromalacia ante mortem," Dissert. inaug. Erlang: Leipzig, 1871.

[1] J. Hunter, "On the Digestion of the Stomach after Death," *Phil. Trans.*: June 18, 1772; and "Observations on Certain Parts of the Animal Economy": London, 1786.

[2] Cl. Bernard, "Leçons de physiologie expérim.," &c., II. p. 406: Paris, 1856.

[3] F. W. Pavy, "On the Gastric Juice," &c., *Guy's Hospital Reports*, vol. ii. p. 265: 1856.

[4] F. W. Pavy, "On the Immunity enjoyed by the Stomach from being digested by its own Secretion during Life," *Phil. Trans.*, vol. cliii. part. i. p. 161: 1863; and "On Gastric Erosion," *Guy's Hospital Reports*, vol. xiii. p. 494: 1868.

The blood brings to the glandular cells everything which is necessary to fulfil their functions. If the supply of blood be cut off, those vital functions which resist the action of the pepsin ferment must also cease. Why does not the pancreas digest itself, as pancreatic ferment is effective in a neutral and alkaline solution?

Here we are face to face with an unsolved problem. But it is not a new one; as the epithelial cells of the gastric glands liberate free hydrochloric acid and still remain alkaline, so the epithelial cells of the pancreatic gland secrete the ferment and themselves remain free from ferment. We see the same thing going on in every vegetable cell. The cell sap which fills up cavities in the protoplasm of the cell is acid, the cell itself, like all contractile protoplasm, is alkaline. The cell sap is frequently brilliantly colored, while the cell itself, which produces the coloring matter, is colorless. But as soon as life ceases, as soon as the vital phenomena, the visible ameboid movements, stop, the incomprehensible power of selecting substances likewise disappears; the laws of diffusion are in no way interfered with, and the protoplasm becomes tinged with coloring matter. This inexplicable power of separating and distributing the substances according to the object in view is possessed by every cell in our bodies (compare above, p. 137).

Pavy relies upon the fact that self-digestion occurred after the introduction of large quantities of acid into the stomach, even when the circulation was not disturbed, to prove his view that circulating blood prevents self-digestion only by its alkalinity. In this case, Pavy considers the alkalies do not suffice to prevent the action of the acids. He injected 3 ozs. (= 93 grms.) of dilute hydrochloric acid, which contained 3 drms. (= 12 grms.) HCl, into the stomach of a dog, and at the same time tied the pylorus and the esophagus, avoiding the vessels. The dog died in an hour and forty minutes, and the post-mortem, which was immediately made, showed solution of the gastric mucous membrane, and perforation of the wall of the stomach at the cardiac orifice. But this experiment does not justify any conclusion. The amount of hydrochloric acid injected was much too large. Pavy might have destroyed the wall of the stomach equally well with caustic potash.

It has often been attempted to refer the origin of the round gastric ulcer to self-digestion. But the danger of self-digestion is by no means so great as was formerly believed. It has been shown, by numerous researches, that the wall of the stomach has a decided tendency to heal rapidly after wounds of the most varied description. This is conclusively proved by the favorable results of operations on the stomach in animals and human beings. The most plausible hypothesis on the cause of the gastric ulcer has been advanced by Virchow,[1] who considers that some kind of disturbance in the circulation is at the root of the disease. And, in fact, Panum [2] succeeded in producing hemorrhagic infarctions with the subsequent formation of ulcers in dogs, by embolic plugging of the smallest arteries of the gastric mucous membrane. These results are quite in harmony with Pavy's above-mentioned experiments. But it has very rarely been found that thrombotic or embolic plugging precedes the round gastric ulcer in human beings. It has therefore been assumed that the round gastric ulcer was caused by abnormal increase of acid in the gastric juice, or in the contents of the stomach. But this supposition is utterly unsupported by fact. It is also to be noted that the gastric ulcer is generally situated in the pylorus and in the small curvature, very seldom in the fundus, where the acidity is greatest. The etiology of the *Ulcus ventriculi* is still involved in obscurity.

I must not omit to mention that one of the functions of the stomach consists in the absorption of nutritive substances. The process undoubtedly commences in this section of the digestive tract. The most recent and careful researches on this function we owe to J. von Mering[3] and his pupils. Mering established duodenal fistulæ in dogs and then introduced water or solutions of food-stuffs into their stomachs. When pure water was given, it flowed out of the fistula even while the animals were drinking, but always in spurts. If the finger were introduced into the pylorus, this intermittent flow was found to be due to the alternate contraction and relaxation of the pyloric orifice. Each minute the pylorus opened two to six times, each time letting out from 2–15 cc. of water. In over 100 experiments, in which a measured quantity of water was given by the mouth, almost the exact amount was recovered from the duodenal fistula, and indeed, on one or two occasions, a few cc. over and above. Thus in one large dog, after 440 cc. water had been taken by the mouth, 445 cc. flowed out from the fistula within the next

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[1] Virchow in his *Arch.*, vol. v. p. 281: 1853.

[2] Panum, Virchow's *Arch.*, vol. xxv.: 1862.

[3] J. von Mering, assisted by Dr. Aldehoff and Dr. Happel, "Ueb. die Function des Magens." Separatabdruck a. d. *Verhandlungen des III. Congresses f. innere Med. zu Wiesbaden*, 1893. For the older work see H. Tappeiner, "Ueber Resorption im Magen," *Zeitschr. f. Biolog.*, vol. xvi. pp. 497–507: 1880; B. von Anrep, "Die Aufsaugung im Magen des Hundes," Du Bois' *Arch.*, pp. 504–514: 1881; R. Meade Smith, *ibid.*, p. 481: 1884 (experiments on frogs).

thirty minutes. Mering concludes from his experiments that practically no water is absorbed from the stomach.

An obvious criticism of these experiments is that no account has been taken of the salivary secretion. A large dog secretes in one hour from 30–90 ccm. of saliva,[1] which gets into the stomach. If, therefore, only just so much water is recovered from a duodenal fistula as has been taken by the mouth, we must conclude that the stomach has absorbed an amount of water equal to the volume of saliva secreted during this time. It is to be hoped that these experiments will be repeated in combination with extirpation of the salivary glands or ligature of their ducts, or that the saliva be prevented in some other way from reaching the stomach. It must be further objected that the stomach behaves quite differently when the fluid is allowed to flow into the intestines instead of escaping by the duodenal fistula. Thus Mering states that "if the duodenal fistula be closed so that the contents of the stomach can only be discharged into the intestine, all escape from the body being prevented, a very much longer time elapses before the ingested water leaves the stomach. Whereas, in a dog with open fistula 500 cc. left the stomach in less than thirty minutes, after closure of the fistula in the same dog a considerable amount of fluid was still found in the stomach sixty minutes after its introduction. If 250 cc. of warm milk be introduced by means of the fistulous opening into the duodenum in the course of fifteen minutes, and then 500 cc. water be injected into the empty stomach, only a few cc. of fluid will leave the stomach within the next half hour; although when the intestine is empty the stomach would get rid of the 500 cc. by means of the fistulous opening in less than thirty minutes. This arrangement evidently indicates that distention of the small intestine reflexly inhibits the evacuation of the stomach."

If the evacuation of the stomach is thus slowed under normal conditions by this reflex mechanism, we must grant the possibility that there may be a considerable absorption of water from the stomach.

In the animals with a duodenal fistula, the absorption of water on the other hand seemed to be extremely slight, as was evident from the fact that "they were continually tormented with thirst. They drank water by the liter, without assuaging their thirst; in fact, the more they drank, the worse grew the thirst, because a small excess of fluid was secreted by the stomach and lost to the body with the ingested fluids."

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[1] Bidder and Schmidt, "Die Verdauungssäfte u. der Stoffwechsel." Mitau and Leipzig, pp. 12 and 13: 1852.

If solutions of food-stuffs—grape-sugar, maltose, cane-sugar, milk-sugar, dextrin, or peptone—were injected into the stomach of such animals, a portion of these substances could not be recovered from the fluid flowing out by the fistula. Thus 20 per cent. of the dextrose and 60 per cent. of the peptones disappeared. When 30 grms. of sodium chlorid in 400 cc. water were introduced, 6.5 grms. of the salt were absorbed in the stomach. The fluid however increased in amount, so that 787 cc. of fluid were collected from the fistula. Dilute solutions of alcohol behaved like the salt solution : a portion of the alcohol disappeared, but the total volume of fluid was largely increased.

The following experiment served also to show that an excretion of water proceeds, *pari passu*, with the absorption of dissolved substances in the stomach. A dog weighing 7 kilos. was morphinized and its pylorus ligatured. 100 cc. of a 66 per cent. solution of dextrose were then injected into the empty stomach and the esophagus ligatured. After nine hours the stomach was found to contain 400 cc. of fluid, with 9 per cent. of sugar.

These interesting experiments of Mering's are extremely suggestive, especially in their bearing on the symptomatology and therapeutics of pyloric stenosis and dilatation of the stomach. For the many new points of view put forward by this author, I must refer my readers to the study of the original.

LECTURE XI

THE PROCESSES OF DIGESTION IN THE INTESTINE—THE PANCREATIC JUICE AND ITS FERMENTATIVE ACTION—FERMENTS IN GENERAL—THE ACTION OF THE PANCREATIC JUICE ON THE CARBOHYDRATES, FATS, AND PROTEIDS—THE NATURE AND SIGNIFICANCE OF PEPTONES

THE time during which different articles of diet remain in the stomach of human beings varies very greatly. It does not depend only on the quality of the food; it also increases with the quantity. The mechanical condition, the degree to which it has been masticated, likewise affects it, as also the intensity of the preceding hunger, and especially the state of the stomach at that moment, a state which depends on many physical and psychical influences. Numerous observations on people with gastric fistulæ[1] have shown that the food remains in a healthy stomach from three to ten hours. In disease the time is often much longer, as modern experience has discovered by means of the stomach-pump. The emptying of the stomach goes on very gradually in small portions at a time. Busch[2] observed this in a woman, who, in consequence of a wound made by a bull's horns, had an artificial anus a little below the duodenum, from which the contents of the stomach oozed out, as they were unable to reach the other opening of the small intestine. The first portions of food appeared in the fistulous opening as early as from fifteen to thirty minutes after being swallowed.

Three new secretions, all of which yield an alkaline reaction, act immediately upon the food when it reaches the intestine; they are the pancreatic juice, the intestinal juice, and

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[1] W. Beaumont, "Experiments and Observations on the Gastric Juice, and the Physiology of Digestion," reprinted from Plattsburgh edition, by Andrew Combe, Edinburgh, 1838; O. von Grünewaldt, "Succi gastrici humani indoles physic. et chem.," &c., Dissert.: Dorpati, 1853; *Ann. Chem. Pharm.*, vol. xcii. p. 42: 1854; E. v. Schröder, "Succi gastrici humani vis digestiva," Dissert.: Dorpati, 1853; F. Kretschy, *Deutsch. Arch. f. klin. Med.*, vol. xviii. p. 527: 1876; Jul. Uffelmann, *Arch. f. klin. Med.*, vol. xx. p. 535: 1877.

[2] W. Busch, *Arch. f. path. Anat. u. Physiol.*, vol. xiv. p. 140: 1858.

the bile. By their means, the chyme, which is the name given to the acid contents of the stomach, is gradually neutralized, and usually presents in the lower part of the intestine a reaction which may be only slightly acid or even occasionally alkaline.[1] We will first consider the action of the pancreas.

The PANCREAS is the digestive gland *par excellence*. Its secretion, so far as we know, has no other action than a digestive one; it effects chemical changes in all classes of food, and prepares them for absorption. The proteids are peptonized, starch is split up into soluble carbohydrates, the fats into glycerin and fatty acids. There is scarcely any animal which does not possess a secretion with an action analogous to that of the pancreatic juice, whereas a gastric digestion is wanting in many vertebrates, *e. g.*, many fishes and even the lowest mammals, echidna and ornithorynchus.[2] The invertebrates have neither a peptic digestion nor have they bile. But a process analogous to pancreatic action has been found wherever it has been sought.[3] It can even be recognized in the lowest organisms, the bacteria: a fluid containing bacteria acts on the three main classes of foods just like the pancreatic juice. The pancreatic ferments have been found absent only in a few intestinal parasites.[4] This is perfectly clear for teleological reasons: the organisms are always floating about in food that has been already digested.

Before proceeding to consider the modes of action of the pancreatic juice in mammals and in human beings, together with the chemical changes which it causes in the three groups of food-stuffs by its ferments, we will first state clearly what is known concerning the nature and character of FERMENTS. We have already made use of the term 'ferment' on several occasions. It is therefore desirable that we should now consider what conception we are to attach to this word.

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[1] On the reaction of the intestinal contents see A. Macfadyen, M. Nencki, and N. Sieber, *Arch. f. exper. Path. u. Pharm.*, vol. xxviii. p. 319: 1891. The earlier literature will be found here. Compare also Schmidt-Mülheim, *Du Bois' Arch.*, p. 56: 1879; and Gley and Lambling, *Revue biol. du Nord de la France*, vol. i.: 1888. [Vaughan Harley, *Journ. Physiol.*, vol. xviii. p. 2: 1895; Moore and Rockwood, *ibid.*, vol. xxi. p. 58: 1897.]

[2] A. Oppel, *Biol. Centralbl.*, vol. xvi. p. 406: 1896.

[3] Hoppe-Seyler, "Ueber Unterschiede im chemischen Bau und der Verdauung höherer und niederer Thiere," Pflüger's *Arch.*, vol. xiv. p. 395: 1877. Compare also the numerous and comprehensive works on this subject by F. Plateau in the years 1874–1877, and the works of Frédéricq and Krukenberg of the same time. An account of the literature on the digestion of the lower animals has been given by Krukenberg, "Vergleichend physiologische Vorträge," II.; "Grundzüge einer vergleichenden Physiologie der Verdauung": Heidelberg, 1882.

[4] L. Frédéricq, *Bulletins de l'Acad. Roy. de Belgique*, sér. 2, t. xlvi. No. 8: 1878.

We will first restrict ourselves to facts derived from observation. Probably no one has ever seen ferments. What can be seen and observed is merely the process of which the hypothetical ferment is the exciting cause. This process consists, in all cases, in the fact that a complex compound splits up into more simple ones, while kinetic energy in the shape of heat is set free. Therefore in all these processes potential energy is converted into kinetic energy. The atoms pass from an unstable into a stable arrangement. Stronger affinities are hereby satisfied. To adopt the terminology already defined (pp. 34–35), the ultimate cause is the potential energy stored up in the complex molecule, the effect is kinetic energy, and then we have to seek the 'exciting cause,' the 'impetus,' the 'liberating force.' These are termed ferments in some cases, but not in all. What therefore have the liberating forces in all these various processes in common, and what distinguishes them from each other? This can be clearly shown by a series of examples.

Glyceryl trinitrate, so-called nitroglycerin, splits up into carbonic acid, water, nitrogen, and oxygen :—

$$2[C_3H_5(ONO_2)_3] = 6CO_2 + 5H_2O + 6N + O.$$

A very considerable amount of heat is developed. A highly unstable atomic arrangement is converted into a stable one. The oxygen, which has a very slight affinity for nitrogen but a very close affinity for carbon and hydrogen, was in the original molecule combined with nitrogen, but in the smaller molecules resulting from the decomposition, is united with carbon and hydrogen. The impetus is given by mechanical means such as a knock or a blow, therefore by motion, or by heat such as a flame, another form of motion. Nitrogen trichlorid splits up explosively with great development of light and heat into nitrogen and chlorin :—

$$NCl_3 + NCl_3 = N_2 + Cl_2 + Cl_2 + Cl_2.$$

Here again the unstable atomic arrangement is converted into a stable one. Stronger affinities are satisfied. For many reasons we are compelled to adopt the conclusion that the elements, in an uncombined state, do not consist of single isolated atoms, but are united into molecules. The affinity of nitrogen atoms to each other, and of chlorin atoms to each other, is obviously stronger than the affinity of chlorin atoms to nitrogen atoms. The impetus to the rearrangement of the atoms is given by some mechanical means or by a rise of temperature. Iodid of nitrogen, the formation of which is analogous to that of nitrogen trichlorid, explodes even more readily, if acted upon by certain periodic movements, wave-motions of a definite velocity and wave-length. It may be shown that it does not explode on a low-toned, but that it does so on a high-toned plate or string. This phenomenon is evidently analogous to the resonance of certain elastic bodies when struck by waves which proceed from another sounding body. This resonance occurs as is well known only with notes of a definite pitch. So that we may also imagine that, if the vibrations which act upon an unstable molecule have a definite wave-length, the atoms of this molecule are thrown into corresponding vibration, and this suffices to overcome the slight attraction of the atoms to one another, and thus to produce a conversion into more stable compounds.

The explosion of the nitrogen trichlorid can also be brought about by contact with various substances, such as phosphorus, phosphorus compounds free from oxygen, selenium, arsenic, some resins (other kinds being inert), non-volatile oils, &c. Here too we might imagine that, from the various molecular vibrations of these substances (which we call heat), we get a certain resultant vibration which coincides in wave-length with that of one of the constituents of the nitrogen trichlorid molecule, and so occasions its decomposition.

Potassium chlorate splits up into potassium chlorid and oxygen. The dissociation is set up by the application of heat. But the rise of temperature need not be nearly so high when certain substances are present, such as peroxid of manganese, ferric oxid, or cupric oxid. The presence of these substances probably so modifies the heat-waves, that the atoms of the potassium chlorate are more easily thrown into responsive vibrations, and thus decomposed.

Peroxid of hydrogen decomposes on contact with platinum, gold, silver, peroxid of manganese, &c. In these cases it is called an effect of contact, or a katalytic effect. We can form the following hypothesis of the process which goes on here, as in the cases above cited: the substance which acts 'katalytically' exercises an attraction on one of the atoms in the unstable molecule. It does not unite with the atom, but the unstable arrangement of the atoms in the molecule is altered to a stable one.

Grape-sugar splits up into alcohol and carbonic acid :—

$$C_6H_{12}O_6 = 2CO_2 + 2C_2H_6O.$$

This change can be shown to be accompanied by a rise of temperature. This is in accordance with the fact that the heat of combustion of alcohol is less than that of the grape-sugar from which the alcohol arose. Thus a part of the potential energy stored up in the sugar is converted through decomposition into kinetic energy, into heat. The atoms of the sugar have passed from a less stable into a more stable arrangement. Stronger affinities have been satisfied. The nature of the liberating force is in this case still unknown. It is known however that the conversion takes place only if two conditions are fulfilled: they are, first, the presence of yeast-cells; and secondly, a certain temperature—from 10° to 40° C. Judging from analogy of the examples already given, we should suppose that here again a form of motion starts the decomposition. The motion might proceed from the vital functions of the cell. But it is likewise conceivable that certain substances are produced in the metabolism of the cell, and that these substances act in a similar manner to the katalytic bodies in the examples adduced above. The yeast-cells are called a 'ferment.' Quite recently Ed. Buchner[1] has shown that the presence of living cells is not necessary in order that fermentation may take place. He finely powdered the cells with quartz sand, treated them with a little water, and then subjected them in an hydraulic press to a pressure of 500 atmospheres. He obtained in this way an almost clear yellow fluid which, on mixture with a solution of cane-, grape-, fruit-, or malt-sugar, set up fermentation within half an hour. When the mixtures were kept in the ice-chest, the fermentation lasted a fortnight. It might be thought that the expressed protoplasm still possessed some vital properties, especially as it has often been found that fragments of protoplasm may still present certain signs of vital activity, such as contraction. In reply to this objection may be set the fact observed by Buchner that the fermentative action of yeast-juice is not abolished by the addition of chloroform, which, as is well known, inhibits all the vital functions with which we are acquainted.

Cane-sugar splits up into equivalent quantities of dextrose and levulose. Here again there is a development of heat,[2] and again the yeast plays a part. But in this case also it is not requisite that the cells should be living; an aqueous extract from the yeast-cells, killed with ether, is all that is necessary. We may assume that the atoms composing any of the molecules in this extract are in a state of oscillation, or that different molecules oscillate against each other, and that the resultant of

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[1] Ed. Buchner, *Ber. d. deutsch. chem. Ges.*, vol. xxx. p. 117: 1897. Compare J. de Rey-Pailhade, *Compt. rend.*, vol. cxviii. p. 201: 1894.

[2] A. Kunkel, Pflüger's *Arch.*, vol. xx. p. 509: 1879.

these motions causes the dissociation of the molecules of cane-sugar. A theory has been advanced, but not yet verified, that the presence of one particular chemical individual in the yeast-extract is essential for the initiation of decomposition. This ferment has been termed invertin.[1] An account of the attempts which have been made to isolate the ferments will be given later.

Starch-flour decomposes on boiling with dilute acid into molecules of grape-sugar. In this reaction the direct proof that heat is produced cannot be given. But we must assume that this is the case, because the heat of combustion of the grape-sugar is less than that of the starch. The impetus to the change may be a special modification of the increased molecular movement due to the heat in presence of the acid; or we must suppose that the acid attracts the sugar molecules contained in the starch molecule, and possibly forms a temporary compound which again rapidly breaks up with absorption of water. The conversion of starch into sugar is always accompanied by hydration, which is the case in the decomposition of cane-sugar, and probably in all similar decompositions. I shall return to this point again.

Starch-flour also splits up at a moderate temperature into maltose and dextrin, if it comes into contact with certain substances, which are contained in germinating barley or in saliva and in pancreatic juice. But in this case the term ferments is used as indicating chemical individuals. But these hypothetical substances are perhaps merely the conditions necessary to start a definite form of motion, which acts as the impetus in the decomposition of the starch-molecule. A development of heat cannot be proved when starch is broken up by ferments. Maly[2] even observed an absorption of heat. This is explicable in the following way: starch-flour is insoluble, whereas the products of decomposition are soluble in water. Heat must be used up in their solution, as is always the case in the transit from the solid to the fluid state. The amount of heat thus fixed is greater than that liberated by decomposition. That heat is set free when decomposition takes place follows of necessity from the fact that the heat of combustion of the maltose and dextrin is less than that of an equivalent amount of starch-flour.

Hoppe-Seyler[3] and his pupils[4] have shown that formate of

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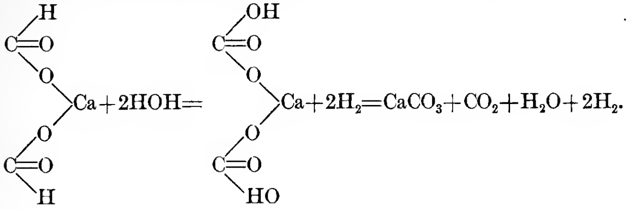
[1] Eduard Donath, *Ber. d. deutsch. chem. Ges.*, vol. viii. p. 795: 1875; vol. xi. p. 1089: 1878; M. Barth, *ibid.*, vol. xi. p. 474: 1878.

[2] Maly, Pflüger's *Arch.*, vol. xxii. p. 111: 1880.

[3] Hoppe-Seyler, Pflüger's *Arch.*, vol. xii. p. 4: 1876.

[4] Leo Popoff, Pflüger's *Arch.*, vol. x. p. 113: 1875.

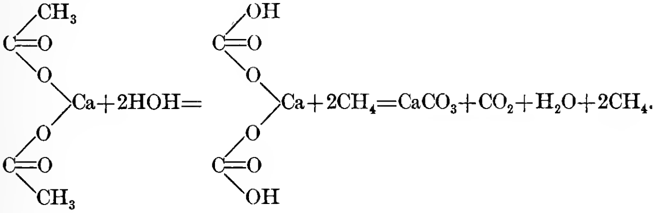
lime, by the action of certain bacteria, is split up into carbonate of lime, carbonic acid, and hydrogen, with absorption of water:—



Heat is developed in this process. If the bacteria be killed by ether, the decomposition continues. This ferment therefore behaves like invertin. Sainte-Claire Deville and Debray[1] have made the important discovery that the same decomposition of formic acid into carbonic acid and hydrogen can be also brought about by finely divided iridium, rhodium, or ruthenium, obtained in a moist condition by reduction. Platinum or palladium produced in the same way had no action.

We thus see that a living cell, an organic substance, and a metal all produce the same effect.

The decomposition of acetic acid into carbonic acid and marsh-gas is completely analogous to the decomposition of formic acid, and occurs under the same conditions:—



Heat must again be set free in this process, for the heat of combustion of the marsh-gas is less than that of an equivalent amount of acetic acid.

From all these examples it may be seen that we know nothing further concerning the ferments than we do about the 'katalytic' substances. Their presence is absolutely essential to bring about that form of motion which gives the impetus to the transition from an unstable arrangement of atoms into a more stable one. We speak of a katalytic effect, when the substance to which this effect is ascribed happens to be a

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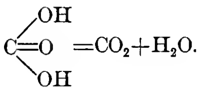
[1] H. Sainte-Claire Deville et H. Debray, *Comp. rend.*, vol. lxxviii. 2, p. 1782: 1874.

well-known inorganic compound or an element. If, on the other hand, they are unknown organic substances, we speak of a fermentative action. There is at present no reason for assuming that there is any essential difference between the mode of action of organized ferments — living unicellular organisms — and non-organized, 'unformed' ferments. We may suppose that the process of fermentation is the same in both cases; but we know as little concerning the action of the unformed ferments as we do concerning the organized ferments.

The decomposition effected by the organized ferments appears to take place in the substance of the living cell, and the energy liberated by the decomposition is utilized for the vital processes of the cell. In favor of this view can be adduced the fact that, in the case of alcoholic fermentation, the amount of sugar decomposed in the unit of time is inversely proportional to the supply of oxygen. With a free supply of oxygen, there are two sources for the production of the kinetic energy required for the vital functions: decomposition and oxidation. When oxygen is withdrawn, one source is closed, and the other utilized the more.[1] This fact is of far-reaching importance for the comprehension of the vital processes in the higher animals.[2]

In all fermentations the decomposition is always accompanied by hydration, in consequence of which these processes can only take place in presence of water. The exceptions to this rule are only apparent. Thus in alcoholic fermentation, grape-sugar ($C_6H_{12}O_6$) is decomposed into $2C_2H_6O$ and $2CO_2$, apparently therefore without taking up any water. But we must not forget that carbonic acid in watery solution must, like all other dibasic acids, contain two HO radicals :—



$$\mathrm{C(OH)_2{=}O} = \mathrm{CO_2 + H_2O}.$$

Butyric acid fermentation ($C_6H_{12}O_6 = C_4H_8O_2 + 2CO_2 + 2H_2$), and lactic acid fermentation ($C_6H_{12}O_6 = 2C_3H_6O_3$) also appear

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[1] Brefeld, *Landw. Jahrb. v. Nathusius u. Thiel*, Heft. i.: 1874; *Verhandl. d. Würzburger phys.-med. Gesellsch.*, N. F., vol. viii. p. 96: 1874; Pasteur, "Études sur la bière," chap. vi. p. 229: Paris, 1876; Hoppe-Seyler, "Ueber die Einwirkung des Sauerstoffes auf Gährungen": Festschrift, Strassburg, 1881; Nencki, *Arch. f. exp. Path. u. Pharm.*, vol. xxi. p. 299: 1886.

[2] The fact observed by A. Fränkel (Virchow's *Arch.*, vol. lxvii. p. 283: 1876), that the decomposition by proteid goes on twice as fast in dogs when their supply of oxygen is diminished, is perhaps of a similar nature. Compare also Herm. Oppenheim, Pflüger's *Arch.*, vol. xxiii. p. 490: 1880.

to form exceptions. From analogy with other processes of fermentation, we must suppose that these processes are also accompanied by hydration. We must refer the reader to the papers of Hoppe-Seyler[1] and Nencki[2] for further information on this subject.

Many attempts have been made to isolate the unorganized ferments. It is in fact possible to obtain precipitates from solutions containing ferments which still retain the characteristic fermentative properties. But we have no guarantee that these precipitates, which are always amorphous, are chemical entities. In the cases in which they have been analyzed, the composition has been found closely similar to that of proteids and peptones. But we cannot ascertain whether the ferment may not form a fraction of the material analyzed, so small as not to influence the result of the analysis.

All ferments are soluble in water; all may be precipitated from their aqueous solutions by alcohol or ammonium sulphate,[3] and are again dissolved by water after their precipitation. Most of them are also soluble in glycerin, and may be precipitated from this solution by alcohol.[4] All the previous attempts at isolation mainly depend on these properties, which are however common to a large number of other constituents of the tissues; so that other means must be found to effect a further separation. Certain ferments—such for instance as pepsin—do not diffuse through animal membranes,[5] and all have a great tendency to be carried down by neutral precipitates.[6] These properties have also been utilized for the purpose of isolating ferments. It would lead us too far to give details concerning all these procedures. I must refer you to the observations of Brücke,[7] Danilewsky,[8] Cohnheim,[9]

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[1] Hoppe-Seyler, Pflüger's *Arch.*, vol. xii. p. 14: 1876.

[2] Nencki, *Journ. f. prakt. Chem.*, vol. xvii. p. 105: 1879.

[3] [Invertin appears not to be precipitated by ammonium sulphate.]

[4] Von Wittich, Pflüger's *Arch.*, vol. ii. p. 193: 1869; and vol. iii. p. 339: 1870.

[5] Krasilnikow, *Medicinisky Wjestnik*: 1864. Diakonow gives a short notice of this work in Hoppe-Seyler's *Med. chem. Unters.*, p. 241. See also A. Schöffer, *Centralbl. f. d. med. Wissensch.*, p. 641: 1866; von. Wittich, Pflüger's *Arch.*, vol. v. p. 443: 1872; Olof Hammarsten, "Om pepsinets indiffusibilitet," *Upsala läkareförennings förhandlingar*, vol. viii. p. 565: 1873.

[6] Brücke, *Sitzungsber. d. Wiener Akad.*, vol. xliii. p. 601: 1861. A. v. Heltzl, "Beiträge zur Lehre der Verdauungsfermente des Magensaftes": Dorpat, 1864.

[7] Brücke, *Sitzungsber. d. Wiener Akad.*, vol. xxxvii. p. 131: 1859; and vol. xliii. p. 601: 1861.

[8] Danilewsky, Virchow's *Arch.*, vol. xxv. p. 279: 1862.

[9] J. Cohnheim, Virchow's *Arch.*, vol. xxviii. p. 241: 1863.

Aug. Schmidt,[1] Hüfner,[2] Maly,[3] Kühne,[4] Barth,[5] and O. Löw.[6]

Every ferment develops its maximum activity at a definite temperature. This temperature must be different in the case of the digestive ferments of cold- and warm-blooded animals; we should expect this on teleological grounds, and it is confirmed by direct observation. By treating the gastric mucous membrane of a mammal, recently killed, with dilute HCl (from 2 to 3 per 1,000), a so-called artificial gastric juice is obtained which rapidly peptonizes all varieties of proteid. At an ordinary temperature this action is mostly very slight, and it ceases entirely at about 10° C. At a temperature of 0° C., not the least trace of digestion goes on. But Fick and Murisier[7] found that the artificial gastric juice, prepared from the stomach of the frog, the pike, and the trout, constantly exerted a peptonizing influence even at 0°. Hoppe-Seyler[8] confirmed these results. He found that artificial gastric juice of the pike digested fibrin more rapidly at 15° C. than at 40°, most rapidly at about 20°. A little above 0° the action was slower than at 15°, but still very marked. Fick and Hoppe-Seyler conclude from these observations that the gastric juice of warm-blooded contains a different ferment from that of cold-blooded animals.

Like pepsin obtained from different sources, we find that the so-called diastatic ferments, which decompose starch, develop their maximum effects at temperatures which vary according to the source from which these ferments are derived. The diastatic ferments of the pancreas and saliva act most quickly at from 37° to 40° C.; that of germinating barley at from 54° to 63° C.[9]

When aqueous solutions containing ferments are heated to more than 70° C., the unorganized as well as the organized ferments are destroyed. The solutions are found to be in-

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[1] Aug. Schmidt, "Ueber Emulsin und Legumin," Dissert.: Tübingen, 1871.

[2] Hüfner, *Journ. f. prakt. Chem.*, vol. v. p. 372: 1872.

[3] Maly, Pflüger's *Arch.*, vol. ix. p. 592: 1874.

[4] Kühne, *Verhandl. des naturhist. med. Vereins zu Heidelberg*, vol. i.: 1876; and vol. iii. p. 463: 1886; Kühne and Chittenden, *Zeitschr. f. Biol.*, vol. iv. p. 428: 1886.

[5] Barth, "Zur Kenntniss des Invertins," *Ber. der deutsch. chem. Ges.*, vol. xi. p. 474: 1878.

[6] Löw, Pflüger's *Arch.*, vol. xxvii. p. 203: 1882.

[7] Murisier, *Verhandlungen der phys. med. Gesellschaft zu Würzburg*, vol. iv. p. 120: 1873.

[8] Hoppe-Seyler, Pflüger's *Arch.*, vol. xiv. p. 395: 1877. Compare also M. Flaum, *Zeitschr. f. Biol.*, vol. xxviii. p. 433: 1892.

[9] J. Kjeldahl, "Meddelser fra Carlsberg Laboratoriet Kjöbenhaven": 1879; Maly's *Jahresbericht für Thierchemie*, p. 382: 1879.

operative, both at this temperature and also when they are again cooled down. On the other hand, when in a dry state, the ferments may be exposed to a very high temperature without losing their power. Hüfner[1] heated his dried pancreatic ferment to 100° C. without causing it to become ineffectual. Alex. Schmidt[2] and Salkowski showed that this was also the case with pepsin. Salkowski[3] heated pepsin to 150° C., and pancreatic ferment and invertin to 160° C. for many hours, and showed that they were still active on cooling and when mixed with water. It was thought that this would serve as a means of distinguishing the unorganized from the organized ferments. But more recent investigations have shown that the spores of certain bacteria can stand a temperature of from 110° to 140° C. without losing life or power of development.[4]

The power of resisting absolute alcohol has also been regarded as characteristic of unformed ferments, and as distinguishing them from formed ferments. But the spores of certain bacteria possess even this power. Koch[5] showed, for instance, that the spores of anthrax bacilli could be kept for 110 days in absolute alcohol without being killed. On the other hand, all spores are apparently killed when subjected for a long period, say thirty days, to ether—a treatment which has not been found to have any effect on the unorganized ferments. Prussic acid, chloroform, benzol, thymol, oil of turpentine, and sodium fluorid,[6] are all supposed to act like ether in killing the organized, and in having no effect upon the unorganized, ferments.

After these preliminary remarks on ferments in general, we will now return to the PANCREATIC JUICE and its fermentative actions. I have already mentioned that the pancreatic juice acts upon all the three main groups of food-stuffs. To explain these three actions, it has been assumed that there are three different ferments, although there is no definite ground for such an assumption. Hüfner,[7] in his numerous attempts to

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[1] Hüfner, *Journ. f. prakt. Chem.*, vol. v. p. 372: 1872.

[2] Alex. Schmidt, *Centralbl. f. d. med. Wissensch.*, No. 29: 1876.

[3] Salkowski, Virchow's *Arch.*, vol. lxx. p. 158: 1877; and vol. lxxxi. p. 552: 1880. Compare also Hüppe, *Mittheil. d. Kaiserl. Gesundheitsamtes*, vol. i.: 1881.

[4] R. Koch, und Wolffhügel, *Mittheil. d. Kaiserl. Gesundheitsamtes*, vol. i.: Berlin, 1881; Max. Wolff, Virchow's *Arch.*, vol. cii. p. 81: 1885.

[5] R. Koch, "Ueber Disinfection," *Mittheil. d. Kaiserl. Gesundheitsamtes*, vol. i.: 1881.

[6] M. Arthus and Ad. Huber, *Arch. d. Physiol.*, vol. xxiv. p. 651: 1894. *Compt. rend.*, vol. cxvi. p. 839: 1894.

[7] Hüfner, *Journ. f. prakt. Chem.*, vol. v. p. 372: 1872. For the experiments to isolate three different ferments, see Danilewsky, Virchow's *Arch.*, vol. xxv. p. 279: 1862; Lossnitzer, "Einige Versuche über die Verdauung der Eiweiss-

isolate the pancreatic ferments, always obtained preparations which had the threefold fermentative action.

With regard to the action on CARBOHYDRATES, the conversion of the insoluble starch flour has been more particularly studied. The process of starch digestion is by no means as simple as it was formerly imagined. Till quite recently, it was considered that starch flour was altered by the digestive ferments of the saliva and of the pancreatic juice, and by the ferment of the germinating barley or diastase, in the same way as on boiling with dilute sulphuric acid, when, as is well known, starch flour is by a process of hydration completely converted into grape-sugar (dextrose), whilst dextrin only occurs as an intermediate stage.

But more recent research has shown[1] that the amount of sugar produced forms but half of the entire weight of the starch, and that this sugar is not grape-sugar, but maltose ($C_{12}H_{22}O_{11} + H_2O$). The remainder is dextrin, and this dextrin cannot be converted into sugar by further action of the ferments. It has also been discovered that there are two varieties of dextrin, of which one is colored red by iodin, while the other remains colorless. It has been further ascertained that a certain carbohydrate, so-called soluble starch, which also gives a blue color with iodin, occurs as an intermediate product between ordinary starch and the dextrins. Finally, it has been found that even the original starch flour is not a chemical entity, but that the concentric layers of the starch granule are composed of various carbohydrates in different proportions.

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körper," Dissert.: Leipzig, 1864; Victor Paschutin, Du Bois' *Arch.*, p. 382: 1873; Kühne, *Verhandl. d. naturhist. med. Ver. zu Heidelb.*, N. F., vol. i.: 1876. Heidenhain and his pupil Podolinski come to the conclusion that the ferment which dissolves proteid does not exist preformed in the pancreas, but is formed during secretion from a precursor present in the gland (Pflüger's *Arch.*, vol. x. p. 557: 1875; and vol. xiii. p. 422: 1876). Compare also Giov. Weiss, Virchow's *Arch.*, vol. lxviii. p. 413: 1876.

[1] Musculus, *Compt. rend.*, vol. l. p. 785: 1860; or *Ann. chim. et phys.*, sér. iii. vol. lx. p. 203: 1860; *Compt. rend.*, vol. lxviii. p. 1267: 1869; vol. lxx. p. 857: 1870; vol. lxxviii. 2, p. 1413: 1874; *Ann. chim. et phys.*, sér. v. vol. ii. p. 385: 1874; Payen, *Ann. chim. et phys.*, sér. iv. vol. iv. p. 286: 1865; L. Coutaret, *Compt. rend.*, vol. lxx. p. 382: 1870; Aug. Schwarzer, *Journ. f. prakt. Chem.*, N. F., vol. i. p. 212: 1870; E. Schulze u. Märker, Dingler's *Polytechnisches Journ.*, vol. ccvi. p. 245: 1872; Brücke, *Sitzungsberichte d. Wiener Akad.*, vol. lxv. part iii. p. 126: 1872; C. O'Sullivan, *Journ. of Chem. Soc.*, ser. ii. vol. x. p. 579: 1872; E. Schulze, *Ber. d. deutsch. chem. Ges.*, vol. vii. p. 1048: 1874; Nägeli, "Beiträge zur Kenntniss der Stärkegruppe": Leipzig, 1874; O. Nasse, Pflüger's *Arch.*, vol. xiv. p. 473: 1877. Musculus und v. Mering, *Zeitschr. f. physiol. Chem.*, vol. i. p. 395: 1878; and vol. ii. p. 403: 1878; Musculus und G. Gruber, *Zeitschr. f. physiol. Chem.*, vol. ii. p. 177: 1878. Compare also the review of works by v. Mering, Du Bois' *Arch.*, pp. 389–395: 1877.

The final products of the decomposition of starch are, at any rate, different in the living organism to those produced by artificial digestion outside the body; the starch appears to be completely converted into grape-sugar. Even in long-continued artificial pancreatic digestion of starch, grape-sugar (dextrose) always occurs together with maltose.[1] Maltose and dextrin cannot be found in the blood and in the tissues,[2] and in the case of diabetic patients, who are unable to destroy the carbohydrates, grape-sugar alone appears in the urine after starch has been eaten.

We know as little concerning the changes that cellulose undergoes in the intestine as we do concerning the fate of dextrin. Outside the body, cellulose is neither altered by the pancreatic juice nor by any other digestive secretion. But, as a fact, a large portion, as we have already seen, disappears in the intestine. I imagine that it is a fermentative action which enables the epithelial cells of the intestine to dissolve the cellulose, and perhaps also to convert the dextrin into sugar. This power has frequently been observed in unicellular bodies. I may refer to the behavior of the Vampyrella, which has already been described (p. 3), and which dissolves the cellulose wall of the algæ. A few authors have adopted the view that the cellulose is not made use of in our body at all as food, but is split up by parasitic bacteria in our intestines into carbonic acid and marsh gas. That such a decomposition of cellulose by bacteria does take place has been incontestably proved by Hoppe-Seyler's experiments,[3] which render it probable that it also occurs in the alimentary canal.[4] But it is doubtful whether all the cellulose that disappears in the alimentary canal is split up in this manner.[5]

The pancreatic juice exercises a fermentative action on FATS similar to that on carbohydrates; decomposition takes

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[1] Musculus und v. Mering, *Zeitschr. f. physiol. Chem.*, vol. ii. p. 403: 1879; Horace T. Brown and John Heron, Leibig's *Annal.*, pp. 204, 228: 1880.

[2] Intimation of the occurrence of colloid carbohydrates in the blood of the portal vein may be found in v. Mering's paper, Du Bois' *Arch.*, p. 413: 1877; and in another by A. M. Bleile, Du Bois' *Arch.*, p. 70: 1879. But only very small quantities are concerned, and perhaps even these only occur occasionally. Bleile's experiments prove that the chief part of the dextrin is converted into sugar, as he observed that, after an exclusive diet of dextrin, the amount of sugar in the portal blood increases.

[3] Hoppe-Seyler, *Ber. d. deutsch. chem. Ges.*, vol. xvi. p. 122: 1883; and *Zeitschr. f. physiol. Chem.*, vol. x. p. 404: 1886.

[4] H. Tappeiner, *Zeitschr. f. Biolog.*, vol. xx. p. 52: 1884; and vol. xxiv. p. 105: 1888.

[5] Compare H. Weiske, *Chem. Centralbl.*, vol. xv. p. 385: 1884; Henneberg and Stohmann, *Zeitschr. f. Biolog.*, vol. xxi. p. 613: 1885; F. Lehmann, *Journ. f. Landw.*, vol. xxxvii. p. 251: 1889; Alf. Mallèvre, Pflüger's *Arch.*, vol. xlix. p. 460: 1891; Zuntz, *ibid.*, vol. xlix. p. 477: 1891.

place with hydration. The fats are well known to be compound ethers, combinations of a trivalent alcohol, glycerin, with three molecules of monobasic acids, principally stearic acid, palmitic acid, and oleic acid. Beside which, certain fats contain small quantities of volatile fatty acids, such as butyric acid in the fats of milk. By the action of the pancreatic ferment, the fat molecule takes up three molecules of water, and splits up into glycerin and into three molecules of fatty acid. This action of the pancreatic juice was discovered by Bernard.[1] How large a portion of the fats is thus broken up in the intestine cannot be stated, but it is probably a very small one. For the decomposition of fats, at least in experiments on artificial digestion, goes on very slowly, whereas the absorption of fats proceeds very rapidly. But it is quite sufficient if only a minute part of the fats is split up, for the whole amount of fat is thereby rendered capable of being converted into a fine emulsion, in which form it passes through the intestinal wall.

The emulsification of fats is brought about in the following manner. It is well known that the neutral fats can only be saponified, *i. e.*, split up into glycerin and salts of fatty acids to form soaps, by free alkalies. Carbonates of the alkalies have no action on neutral fats but only on free fatty acids; the carbonic acid is driven out of the salts by the stronger acid, and a salt is formed by the combination of the fatty acid with alkali. Fatty acids and neutral glycerides are intimately miscible in every proportion. In such a mixture of fat and a small quantity of fatty acid, the molecules of the fatty acid are thus always to be found among the molecules of the neutral glycerids. If a solution of carbonate of soda act upon this mixture, a soapy solution is formed everywhere between the molecules of the neutral fats. By this means the whole mass of fat is immediately converted into a fine emulsion of microscopically small drops. Perfectly fresh neutral fat cannot be emulsified by a solution of carbonate of soda. If, on the other hand, rancid fat be taken, *i. e.*, fat in which a part of the fatty

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[1] Bernard, *Ann. de Chim. et de Physique*, sér. iii. t. xxv. p. 474: 1849. Compare also Ogata, Du Bois' *Arch.*, p. 515: 1881. According to this investigation, which was carried out in Ludwig's laboratory, the decomposition of the fats begins already in the stomach. Marcet had previously come to the same conclusion (*Medical Times and Gazette*, new ser., vol. xvii. p. 210: 1858). The decomposition of fats in the stomach is probably effected, not by an unorganized ferment of the gastric juice, but by putrefactive organisms. The cause of the decomposition of fats in artificial pancreatic digestion has been so interpreted. But Nencki's latest experiments (*Arch. f. exper. Path. u. Pharm.*, vol. xx. p. 373: 1886) show that the pancreatic ferment decomposes as much fat if phenol be present as if there were no antiseptic.

acids has already been set free by the action of putrefactive ferments, or if a small amount of free fatty acids be added to the neutral fat, the emulsion is at once formed. When rancid oil is poured on to a dilute solution of sodium carbonate, the two layers of fluid combine directly they are gently shaken, and the whole is converted into an opaque, uniform, and milky-looking liquid. Under the microscope the fat is seen distributed in minute drops.

There are other alkaline salt solutions which can, like the carbonates of soda or of potash, combine with free fatty acids to form soaps. Such, for instance, is the phosphate of soda with the formula Na_2HPO_4. This salt with fatty acids gives soap and acid phosphate of sodium, NaH_2PO_4. As we shall soon see, the bile, which contains alkaline salts, acts in a similar manner on fatty acids.[1] The emulsions, which are formed by means of bile, are however very temporary.

Carbonate of soda is contained in the pancreatic secretion, for the analysis[2] of the ash shows that the secretion contains more sodium than is necessary for the saturation of the strong mineral acids present. Two weak acids divide the remainder among themselves: proteid and carbonic acid. The intestinal juice is likewise very rich in carbonate of soda, as we shall soon see. By the action of these alkaline secretions the fat is emulsified in minute particles which, as previously described (p. 164), are passed on to the commencement of the chyle-vessels by the active intervention of the epithelial cells.

The mechanism of fat absorption is not however entirely explained by the above-mentioned facts. Some other unknown part must be played by the pancreatic juice in this process, since after extirpation of the pancreas in dogs the absorption of fat is entirely abolished, although the greater part is split up into fatty acids and glycerin, probably by bacterial putrefaction. All the fat eaten by the dogs can be recovered from the feces, partly unchanged, but for the most part as free fatty acids and soaps. If some pig's pancreas be given to the dogs along with

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[1] The emulsifying action of alkaline salt solutions has long been known to technical chemists; it is practically employed in dyeing articles Turkey red. Marcet was the first to draw attention to its physiological bearing (*Medical Times and Gazette*, new ser., vol. xvii. p. 209: 1858). Also Brücke, *Sitzungsber. d. Wiener Akad. Math.-nat. Classe*, vol. lxi. part ii. p. 362: 1870. Compare also J. Steiner, Du Bois' *Arch.*, p. 286: 1874; Joh. Gad, *ibid.*, p. 181: 1878; Georg Quincke, Pflüger's *Arch.*, vol. xix. p. 129: 1879; and Max v. Frey, Du Bois' *Arch.*, p. 382: 1881.

[2] Bidder and Schmidt, "Die Verdauungssäfte u. der Stoffwechsel," p. 245: Mitau and Leipzig, 1852. The sulphuric acid given in the analysis must not be taken into consideration, because it was produced from the sulphur of the proteids only in incineration.

the fat, a portion of the latter is absorbed.[1] Moreover, Claude Bernard has already shown that a pancreatic emulsion differs from other emulsions in that it is not destroyed by a slightly acid medium.

It now only remains to consider the action of the pancreatic secretion on the third main group of food-stuffs, the PROTEIDS. By the action of the pancreatic ferment, as well as that of the gastric ferment, the proteids lose their colloid character; they become diffusible,[2] and are no longer coagulable; they are converted into PEPTONES. The gelatin-yielding substances undergo a similar alteration; they become dissolved, and the solutions lose the power of forming a jelly in the cold.[3]

The peptonizing action of the pancreatic juice was for a long time doubted, until Corvisart[4] decided the matter in the affirmative. Kühne, who was present at Corvisart's experiments, afterwards carried out a series of exhaustive experiments on the subject in Germany.[5] Kühne obtained the secretion from eleven dogs with a temporary pancreatic fistula, and he found that "amazing quantities of boiled fibrin and proteid were dissolved by the juice without any trace of putrefaction, in from half an hour to three hours, at a temperature of 40° C., so that the larger portion was converted into a substance not coagulable at boiling heat, which was readily diffusible through vegetable parchment."

When a fresh pancreas was cut up into small pieces with scissors, mixed with a large quantity of fibrin and water heated to 40° C., and left to stand from three to six hours, the gland disappeared with the fibrin, leaving but a trace behind. The reaction after complete solution was alkaline. Only a small portion of the decomposed proteid could be precipitated

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[1] M. Abelmann, "Ueb. d. Ausnützung d. Nahrungsstoffe nach Pankreasexstirpation." Dissert.: Dorpat, 1890. Compare also Vaughan Harley, *Journ. Physiol.*, vol. xviii. p. 1: 1895; E. Hédon and J. Ville, *Arch. d. Physiol.*, p. 606: 1897; and Hédon, *ibid.*, p. 622. [It should be mentioned here that, according to most authorities at the present time, the greater proportion at any rate of the fat is absorbed by the intestinal wall, not in a particulate condition but in solution, either as fatty acid or as soap. The chief function of the bile seems to be to act as a solvent of these two classes of bodies, and therefore as a carrier of them into the intestinal mucous membrane, where they, with the glycerin, are recombined to form neutral fats.]

[2] The proofs of the power of ready diffusion possessed by peptones have been disputed. See von Wittich, *Berliner klin. Wochenschr.*, No. 37: 1872.

[3] See Fr. Hofmeister, *Zeitschr. f. physiol. Chem.*, vol. ii. p. 299: 1878. An account of the older literature will also be found here.

[4] Corvisart, "Sur une fonction peu connue du pancreas; la digestion des aliments azotées," *Gaz. hebdom.*, Nos. 15, 16, 19: 1857.

[5] W. Kühne, Virchow's *Arch.*, vol. xxxix. p. 130: 1867.

by acetic acid and by boiling.[1] The solution, when filtered, was concentrated at from 60° to 70° C. to one-sixth of its volume and mixed with 95 per cent. of alcohol. This precipitated the peptones in flocculent masses. When the filtered solution was concentrated and cooled down, tyrosin first separated out in crystals; then, on further concentration, leucin crystallized out, in clumps—"leucin cones."

382 parts of dried fibrin and 14.2 parts of dried pancreas yielded—

$$\left.\begin{array}{l}11.0 \text{ undissolved remainder}\\ 42.0 \text{ coagulated proteid}\end{array}\right\}53.5$$

$$\left.\begin{array}{l}211.2 \text{ peptone}\\ 13.3 \text{ tyrosin}\\ 31.6 \text{ leucin}\end{array}\right\}256.1$$

$$397.2 - 53.5 = 343.7 \text{ dissolved proteid.}$$

From this it appears that 100 parts of fibrin gave 61 of peptone, 3.9 of tyrosin, 9.1 of leucin, and 26 of products that we are at present unacquainted with.[2]

It might be supposed that the amido-acids, leucin and tyrosin, are not split off from the proteid molecule by the action of a pancreatic ferment, but by the fermentative action of putrefactive organisms. The pancreas and its juice are substances eminently prone to putrefaction, and the alkaline reaction is favorable to the development of putrefactive organisms. It is this liability to putrefaction which makes it so much more difficult to carry out experiments on artificial pancreatic digestion that on gastric digestion. We know, in fact, that peptones and amido-acids are formed from proteids by the action of putrefactive organisms. But Kühne meets this objection by experiments,[3] which were carried out with

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[1] For an account of the globulin, acid albumin, parapeptone, propeptone, albumoses, &c., which occur in the conversion of proteid into peptone, both in pancreatic and gastric digestion, see Meissner, *Zeitschr. f. rat. Med.*, III. Reihe. vol. vii. p. 1: 1859; Brücke, *Sitzungsber. der Wiener Akad.*, vol. xxxvii. p. 131: 1859; Kühne and Chittenden, *Zeitschr. f. Biolog.*, vol. xix. p. 159: 1883; vol. xx. p. 11: 1884; vol. xxii. p. 409: 1886; R. Herth, *Monatshefte f. Chem.*, vol. v. p. 266: 1884; Kühne, *Verhandl. d. nat. med. Vereins zu Heidelb.*, N. F., vol. iii. p. 286: 1885; Schmidt-Mülheim, Du Bois' *Arch.*, p. 36: 1880; Hans Thierfelder, *Zeitschr. f. physiol. Chem.*, vol. x. p. 577: 1886; R. Neumeister, *Zeitschr. f. Biolog.*, vol. xxiii. pp. 381, 402: 1887; and "Ueb. d. nächste Einwirk. gespannter Wasserdämpfe auf Proteïne," &c.: München, 1889; E. P. Pick, "Zur Kenntniss d. peptischen Spaltungsprodukte des Fibrins," *Zeitschr. f. physiol. Chem.*, vol. xxviii. p. 219: 1899.

[2] [Among these products are to be found the same substances as those which occur in the disintegration of proteids by strong acids, *e. g.*, glutamic and aspartic acids, as well as the hexone bases, argenin, lysin, and histidin.]

[3] Kühne, *Verhandl. d. naturhistor. med. Vereins zu Heidelb.*, N. F., vol. i. Heft iii.: 1876.

the use of salicylic acid as an antiseptic. He showed that concentrated salicylic acid, while arresting the development of putrefactive germs, does not inhibit the action of the pancreatic ferment, and that amido-acids are still formed under these conditions.

Kühne is of opinion that amido-acids are also formed in the intestine of living animals. He tied the intestine of a live dog above the entrance of the pancreatic duct, and again four feet lower down, introduced canulæ at the upper and lower extremities of the intestine he had tied, and passed a stream of water heated to 40° C. through it until it was quite clean. Fibrin was then put in the piece of intestine, and the wound in the abdomen was closed. The dog was killed after four hours, and the piece of intestine cut out. Among the contents were found peptone, tyrosin, and leucin.

It may be *à priori* doubted on teleological grounds, whether under normal conditions the amount of amido-acids formed in the intestine is a large one. It would be a waste of chemical potential energy, which would serve no purpose when converted into kinetic energy by their decomposition, and a reunion of the products of such a profound decomposition outside the intestinal wall is highly improbable. And indeed Schmidt-Mülheim,[1] in numerous experiments on the intestinal contents of dogs fed on meat, could find only traces of amido-acids or else none at all. In the same way Nencki found neither leucin nor tyrosin in the intestinal contents obtained from the fistula of the lower end of the small intestine in the case previously mentioned.[2]

On boiling proteids with dilute acids and alkalies, peptones again appear at first, and amido-acids later on.

We will now inquire into the nature of the process by which proteid is converted into peptone.

As peptone occurs as an intermediate stage in the formation of such decomposition-products as amido-acids from proteid, it may reasonably be imagined that the peptones are the first immediate products of decomposition. This view is further confirmed by the analogy of fermentative action and of the action of acids and alkalies on complex organic compounds of known composition. In all these processes disintegration is accompanied by hydration. The same pancreatic ferment which, accompanied by hydration, splits up the fats into glycerin and fatty acids, and starch flour into dextrin and

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[1] Schmidt-Mülheim, Du Bois' *Arch.*, p. 39: 1879.

[2] Macfadyen, Nencki, and Sieber, *Arch. f. exper. Path. u. Pharm.*, vol. xxviii. p. 323: 1891.

sugar—this same ferment also changes the proteids into peptones. What is more natural than to conclude that the peptones are also formed from the proteids by a process of decomposition accompanied by hydration?

It is a very seductive theory to assume that the colloid and insoluble proteids are polymeric products of the soluble peptones, just as the colloid and insoluble carbohydrates, such as glycogen, gum, starch, or cellulose, are polymeric products of the soluble sugars, and that the peptone molecules after absorption are again combined into proteid molecules, just as the sugar molecules are united to form glycogen in animal tissues, or starch and woody fiber in vegetable tissues. But it must be remembered that this theory is only based upon analogy. At present nothing certain is known about the nature of peptones. It is not known whether the peptones are decomposition-products of proteid, or even whether the decomposition-products themselves are alike or differ from each other, or whether the peptones have arisen from proteid either by a rearrangement of atoms without alteration of the size of the molecules, or by hydration.

In experiments on the composition of peptones, the error has always been made of using impure material. The proteid chosen for the production of peptone has generally been the fibrin of the blood (compare Lecture XIV.). We do not know how many different proteids there are in the coagulum of fibrin; but we know for certain that the nuclei and remains of the broken-up leucocytes, as well as whole leucocytes and the stromata of red blood-corpuscles, are all contained in this coagulum. This method of subjecting a conglomeration of substances and organisms to elementary analysis, and of afterwards comparing the result of the analysis of a mixture of the products of our experiment, can lead to no satisfactory conclusions. But this is the type of some of the most exact work on peptone.[1] Now that we are in a position to produce crystalline proteid compounds, all experiments on the composition of peptones which are made on other material are utterly worthless.

As it has not been found possible to crystallize the peptones from their solutions, or to produce compounds capable of crystallization, or even compounds of constant composition, Maly[2] has adopted the method of fractional precipitation, in order to decide the question whether the peptone solution, obtained from the blood-fibrin by artificial pepsin digestion, contains

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[1] Compare R. Maly's critique in Pflüger's *Arch.*, vol. xx. p. 315: 1879.

[2] R. Maly, Pflüger's *Arch.*, vol. ix. p. 585: 1874.

a single peptone or a mixture of different peptones. Maly treated the clear and highly concentrated peptone solution with strong alcohol, until a portion of the peptone separated out in flocculent masses (fraction 1); the filtrate was again precipitated out with alcohol (fraction 2); and, finally, the remaining alcoholic solution was evaporated to dryness (fraction 3). If the peptone solution contained several different peptones, we should expect to find that the various fractions possessed a varying composition; for we cannot assume that the different peptones have the same power of dissolving in dilute alcohol. Maly found that the figures were so nearly the same in the ultimate analysis of his three fractions, that he came to the conclusion that only one peptone was formed. Maly's pupil, Herth,[1] came to the like conclusion, from experiments carried out on the same principle with solutions of peptone obtained from egg-albumin.

Maly's and Herth's figures have not convinced me of the justice of this conclusion. It is particularly to be regretted that, in the ultimate analyses, the amounts of sulphur in the fractional precipitations were not determined. We should most readily have expected to see a difference in the amount of sulphur. If we regard the proteids as compounds of the peptones, we must assume that there are several peptones, some rich and some poor in sulphur, or else some containing sulphur and others without any sulphur, for the reason that the amount of sulphur in the different kinds of proteid varies so remarkably. But if, on the other hand, we do not regard the peptones as produced by the splitting of the proteid molecule, we must assume as many different peptones as there are proteids of varying composition. There are, at any rate, several peptones. A. Krüger[2] has recently made analyses of proteid and peptones, in which he has bestowed especial care upon the estimation of sulphur; but unfortunately, instead of using pure material, he employed fibrin and egg-albumin. The latter, like the proteid of blood-serum (*vide* Lecture XIV.), is a mixture of at least two different kinds of proteid, a globulin and an albumin.

The quantitative estimates of the amounts of carbon, hydrogen, and nitrogen in the purest of the peptone preparations hitherto made, have always given figures which are

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[1] Robert Herth (Maly's laboratory in Graz), *Zeitschr. f. physiol. Chem.*, vol. i. p. 277: 1887. Compare also A. Henninger, "De la nature et du rôle physiologique des peptones": Paris; *Compt. rend.*, vol. lxxxvi. pp. 1413, 1464: 1878.

[2] Albert Krüger, Pflüger's *Arch.*, vol. xliii. p. 244: 1888. This paper contains a summary of the earlier literature on the amount of sulphur in the various kinds of proteid and the different ways in which sulphur is combined.

within the limits between which the composition of proteid varies.[1]

Whether all proteid, in order to become absorbed, must be previously peptonized, or whether a part is taken up unaltered; whether the peptones are again reconverted into proteid after absorption, and where this conversion takes place;—are questions which will be treated more in detail in Lecture XIII., after we have become acquainted with the parts played by the remaining digestive secretions, the intestinal juice and the bile.

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[1] The divergence in the results recently obtained by Kühne and Chittenden awaits further investigation (*Zeitschr. f. Biolog.*, vol. xxii. p. 423: 1886). It was attempted to obtain further insight into the nature of peptones by comparative experiments on the optical characteristics of the proteids and peptones, on their refractive power, and their behavior towards polarized light. But these investigations have not led to any unanimous or conclusive results (see J. Béchamp, *Compt. rend.*, vol. xciv. p. 883: 1882; A. Poehl, "Ueber des Vorkommen u. die Bildung des Peptons ausserhalb des Verdauungsapparates u. über die Rückbildung des Peptons in Eiweiss," Dorpater Dissert.: St. Petersburg, Röttger, 1882; and *Ber. d. deutsch. chem. Ges.*, p. 1152: 1883). The fact observed by Danilewski, that the heat of combustion of the peptones is less than that of the proteids (*Centralbl. f. d. med. Wissensch.*, Nos. 26 and 27: 1881), can also be interpreted in several ways. This fact agrees with the decomposition hypothesis just as well as with the theory that hydration is the essence of peptonization. It has been, moreover, quite lately noted that the peptones could be reconverted into proteids by the action of dehydrating agents. But all these statements bear the character of preliminary communications. They are not therefore suitable for critical discussion in a text-book. See Henninger, *Compt. rend.*, vol. lxxxvi. p. 1464: 1878; Hofmeister, *Zeitschr. f. physiol. Chem.*, vol. ii. p. 206: 1878; and vol. iv. p. 267: 1880; Danilewski, *Centralbl. f. d. med. Wissensch.*, No. 42: 1880; Schmidt-Mülheim, Du Bois' *Arch.*, p. 36: 1880; A. Poehl, *loc. cit.*, and *Ber. d. deutsch. chem. Ges.*, p. 1355: 1881; p. 1163: 1883. Compare also O. Loew, Pflüger's *Arch.*, vol. xxxi. p. 405: 1883; and R. Neumeister, *Zeitschr. f. Biolog.*, vol. xxiii. p. 394: 1887.

LECTURE XII

INTESTINAL JUICE AND BILE

THIRY,[1] by his bold vivisection, was the first to obtain and examine the INTESTINAL JUICE, the secretion of Lieberkühn's glands, in a pure state. Thiry opened the abdomen of dogs, after they had fasted for twenty-four hours, by an incision in the linea alba. A coil of small intestine was drawn out, and a piece from 10 to 15 cms. in length was resected without injury to the mesentery. The edges of the two ends of the intestine were sewn together in the usual way. One end of the resected piece of intestine was closed with crossed sutures and replaced; the other end, left open, was sewn into the abdominal wound. Although Thiry did not treat the wound antiseptically, he succeeded in preventing peritonitis in a few cases, and in getting the wound to heal quickly. In from two to five days the animals could again receive food into their shortened intestine, and remained in good health for months. Quincke[2] has repeated these experiments several times; one of the dogs experimented upon lived for nine months after the operation, and died from an accident. An abundant secretion of intestinal juice was brought about in this isolated piece of intestine by mechanical and chemical stimulation, especially by acids. The juice was readily obtained for examination by putting in small pieces of sponge, which were removed after a time and squeezed out.

To the obvious objection that a secretion thus obtained was not normal intestinal juice, Thiry and Quincke replied with the following arguments: 1. The microscopic examination of the intestinal wall showed no changes in its histological structure as a whole, or in Lieberkühn's glands, even several months after the operation. 2. The circulation in the mesentery and the innervation did not appear to be disturbed; the reflex mechanism was maintained. 3. Intestinal parasites continued to live in the isolated piece of intestine: a *Nematode* and a *Tenia*

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[1] Thiry, *Sitzungsber. d. Wiener Akad.*, vol. l. p. 77: 1864.

[2] H. Quincke, Du Bois' *Arch.*, p. 150: 1868. Compare also Leube, *Centralbl. f. d. med. Wissensch.*, p. 289: 1868.

serrata, the latter of which from time to time cast off ripe segments. This last argument is rendered convincing by the fact that these creatures exist only under certain conditions, and that most kinds of intestinal worms live only in certain portions of the alimentary canal of definite animal species.

The secretion obtained from the isolated piece of intestine proved to have no action on any of the three main groups of organic food-stuffs; fats and starch flour remained unaltered. Of the proteids, according to Thiry, only the blood-fibrin was dissolved, but no other kinds of proteid, such as bits of meat or coagulated egg-albumin; gelatin did not lose its power of gelatinizing. Quincke could not even confirm the action of the secretion upon fibrin; he found the intestinal juice quite inactive on all food. Lehmann[1] also came to the same conclusions, when he examined the secretion from an isolated piece of goat's intestine. Many further experiments on artificial digestion have been carried out with extracts from the intestinal mucous membrane of various animals. In these experiments there was either no action to be observed on any article of diet, or a very slight one only on boiled starch flour, when sugar was formed. But no importance should be attached to the last results, as a ferment with a slow action upon boiled starch may be extracted from every tissue.

Lastly, Demant[2] has more recently made experiments on the action of the intestinal juice in human beings. Demant had the opportunity of collecting pure intestinal juice from the lower portion of intestine, in a case of artificial anus after herniotomy, which occurred in Leube's hospital-practice in Erlangen. A part of the intestine bulged out like a sausage from the fistulous opening (of which there were two) belonging to the lower portion of the intestine. Usually but little juice oozed out of this opening; the supply was however abundant after meals, and could be collected in a glass beaker which was held underneath without touching the intestinal mucous membrane. In this manner, from 15 to 25 c.cms. of the secretion were obtained in the course of one day. The secretion thus occurred without any direct chemical or mechanical stimula-

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[1] Karl B. Lehmann, Pflüger's *Arch.*, vol. xxxiii. p. 180: 1884. Compare also J. Wenz, *Zeitschr. f. Biolog.*, vol. xxii. p. 1: 1886; Fr. Pregl, Pflüger's *Arch.*, vol. lxi. p. 359: 1895. L. Vella obtained different results on repeating Thiry's experiments on dogs (Moleschott's *Unt. zur Naturlehre*, &c., vol. xiii. p. 40: 1881); he found that the juice acted on all the main groups of food-stuffs. This divergence of opinion does not as yet admit of explanation.

[2] Bernh. Demant, Virchow's *Arch.*, vol. lxxv. p. 419: 1879. Compare the observation of a similar case by H. Tubby and T. D. Manning, *Guy's Hosp. Reports*, p. 271: 1892.

tion of the mucous membrane, merely from the normal reflex irritation, which proceeded from the upper portions of the alimentary canal. It is therefore probable that Demant really obtained the normal secretion, and not an inflammatory transudation of mucous membrane, brought about by abnormal irritation.

The intestinal juice of man, experimented upon by Demant, appeared to produce no change in any form of proteid, nor in fibrin and fats. It had a very slight action on boiled starch, which in numerous experiments never occurred till five hours had elapsed, at from 36° to 38° C. No trace of sugar could be detected before this time had passed.

If the intestinal juice has no action upon food, of what importance is it? Will not its chemical composition enlighten us here? Quincke found that it contained remarkably little of any organic constituents; in fact, only 0.5 per cent., which was chiefly proteid. Thiry found somewhat more. Both investigators agree that the amount of inorganic salts was 0.9 per cent.; among these carbonate of soda is the chief. Both Thiry and Quincke remarked that the intestinal juice effervesces on the addition of acids, and the same thing has been noticed by Demant with the human secretion.

The importance of the intestinal juice lies undoubtedly in the large amount of carbonate of soda it contains. Its function is to neutralize the acids of the intestinal contents, and to emulsify the fats with the surplus carbonate of soda (compare above, p. 165). It has to supersaturate not only the hydrochloric acid of the gastric juice, but also the acids, sometimes existing in far larger quantities, which arise from the butyric and lactic acid fermentations. The rapidity of the passage of the carbonate of soda through the intestinal wall must therefore be proportionate to the acidity of the intestinal contents. For as soon as the carbonate of soda became over-saturated, the absorption of fat would necessarily be at a standstill [assuming that emulsification is a necessary preliminary to absorption]. This is prevented by reflex mechanism. Thiry and Quincke observed that, on stimulating the intestinal mucous membrane with acids, the secretion of the alkaline intestinal juice at once became more copious.

To this interpretation, that the emulsifying and absorption of fats is brought about by the carbonate of soda in the intestinal juice, the objection has been raised that the absorption of fats begins early in the upper part of the intestine, where the reaction of the intestinal contents is always acid. Further, it is well known that during digestion the chyle-vessels in the duodenum become opaque and white, through being filled with droplets of fat, and also that the contents of the entire small intestine as far as the cecum occasionally give an acid reaction.[1] To this I would reply, that it is not the reaction of the internal part of the food-mass which is of importance, but the reaction of its surface which comes in contact with the absorbing intestinal wall. That this latter always remains alkaline is due to the above-mentioned reflex mechanism.

It appears to me that the carbonate of soda in the intestinal juice also serves another purpose. The food absorbs hydrochloric acid in the stomach; the molecules of hydrochloric acid are distributed among the minutest particles of organic food. When the sodium carbonate neutralizes the acid, the carbonic acid thus liberated effectually separates the minute particles of the organic food from each other. The bulk of the food is more thoroughly broken up, and the digestive ferments gain more complete and easy access to the individual particles, and so effect the rapid solution of the food in the intestine.

In conclusion, I must not omit to mention that another explanation has been given by Hoppe-Seyler of the action of the intestinal juice, which is opposed to mine. Hoppe-Seyler's[2] view is that probably no special intestinal juice exists as a secretion of Lieberkühn's glands, or of the intestinal mucous membrane; at any rate, he sees at present no proof of its existence. He thinks that, the quantitative composition of the supposed intestinal juice being identical with that of the blood-plasma and of lymph, we cannot regard the fluid obtained from Thiry's intestinal fistula as being anything but a transudation brought about by abnormal stimulation.

In reply, I would merely ask how we are to explain the fact that the intestinal contents, which give an acid reaction in the upper portion of the small intestine, even after admixture with the pancreatic juice and with bile, are nearly always markedly alkaline[3] in the lower portion of the intestine, and this in spite of the incessant lactic and butyric acid fermentations.

Hoppe-Seyler teaches that the recesses of the intestines, designated as Lieberkühn's glands, serve only to enlarge the absorbent intestinal surface, and that the supposed glandular epithelium is only a continuation of the absorbent epithelium

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[1] Th. Cash, Du Bois' *Arch.*, p. 323: 1880.

[2] Hoppe-Seyler, "Physiologische Chemie," pp. 270, 275: Berlin, 1881. Compare Arthur Hanau, *Zeitschr. f. Biolog.*, vol. xxii. p. 195: 1886.

[3] Gley and Lambling, *Rev. biol. du Nord de la France*, vol. i.: 1888.

of the villi. On the other hand, Heidenhain[1] asserts that the epithelium of Lieberkühn's glands differs very much morphologically from the epithelium of the villi, and that, as the intestinal contents never penetrate into Lieberkühn's glands, these could not serve for absorption.

The BILE, the secretion of the liver, is the only secretion poured into the alimentary canal which remains for our consideration. The secretion of bile is not the only function of the liver. This is soon seen by comparing the size of the liver and the small amount of bile produced with the size of other glands and the quantity of their secretions. The human liver weighs from 1500 to 2000 grms., and produces in twenty-four hours about 400 to 800 grms. of bile.[2] The parotid, which weighs only from 24 to 30 grms., produces in the same time from 800 to 1000 grms. of secretion. This simple fact shows that the liver probably has other functions to perform. We must refer our readers to another lecture (Lecture XXII.) for an account of the numerous and complicated chemical processes that go on in this the largest of all the glands, and of the origin of the bile from the constituents of the blood. At present we have only to do with the secretion, when affected, and its significance in intestinal digestion.

The digestive secretions which have been under consideration do not contain any specific constituents, if we exclude the ferments which we are unable to isolate. So far as our knowledge goes, they consist only of substances which are distributed all over the body. The chief solid constituents of the bile, on the other hand, are found to consist of specific organic compounds, which are either not met with at all elsewhere in

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[1] Heidenhain, *Pflüger's Arch.*, vol. xliii. Sup. p. 25: 1888.

[2] For the method of establishing a biliary fistula, and of determining the amount of bile produced in twenty-four hours, see Schwann, *Arch. f. Anat. u. Physiol.*, p. 127: 1844; Blondlot, "Essai sur les fonctions du foie," &c.: Paris, 1846; Bidder and Schmidt, "Die Verdauungssäfte u. der Stoffwechsel," p. 98; Leipzig and Mitau, 1852. The amount of bile secreted in twenty-four hours in cases of men with biliary fistulæ, was estimated by J. Ranke, "Die Blutvertheilung und der Thätigkeitswechsel der Organe," pp. 39, 145: Leipzig, 1871; v. Wittich, Pflüger's *Arch.*, vol. vi. p. 181: 1872; Westphalen, *Deutsch. Arch. f. klin. Med.*, vol. xi. p. 588: 1873; Gerald F. Yeo and E. F. Herroun, *Journ. of Physiol.*, vol. v. p. 116: 1884. Copeman and Winston, *Journ. Physiol.*, vol. x. p. 213: 1889. Mayo Robson, *Proc. Roy. Soc.*, vol. xlvii. p. 499: 1890; Noel Paton and J. M. Balfour, *Rep. Lab. Roy. Coll. Phys., Edin.*, vol. iii. p. 191: 1891. The amount of bile in twenty-four hours estimated in the case of men with biliary fistulæ is certainly too small, for the ductus choledochus was open, and a part of the bile escaped into the intestine. With animals where the ductus choledochus had been tied, a far larger amount of bile was obtained proportionate to their weight. Bidder and Schmidt (*loc. cit.*, pp. 114–209) found from 13 to 29 grms. of bile in twenty-four hours to every kilogramme of weight, in the case of dogs; with cats, an average of 14.5; sheep, 25.4; rabbits, 136.8.

the animal body or only in traces. We will therefore proceed to examine these compounds more closely.

The sodium salts of two complex acids form the chief constituents of the bile; glycocholic acid and taurocholic acid. The former of these acids splits up, on boiling with acids and alkalies as well as when acted on by ferments with hydration, into an acid free from nitrogen, cholalic acid, and into a substance containing nitrogen, glycocoll. The taurochloric acid splits up, by the same means, into cholalic acid, and into a body containing both nitrogen and sulphur, taurin.[1]

In spite of numerous investigations,[2] little is known concerning the constitution of cholalic acid. It appears that the cholalic acids from the biliary acids of various animals have a different composition, although possessing similar physical and chemical qualities. The formula for the cholalic acid of human bile was found by H. Bayer to be $C_{18}H_{28}O_4$, while that of the cholalic acid in bullock's bile was found to be $C_{24}H_{40}O_5$.

The constitution of glycocoll (glycin) is accurately known. This substance can be synthetically produced from monochloracetic acid and ammonia, and is therefore the same as amido-acetic acid—$CH_2(NH_2)COOH$. It cannot be traced in a free state in the animal body, but occurs in combination with another acid than cholalic acid, as hippuric acid. We shall soon meet with it again. It undoubtedly originates in the animal body from proteid. It can be artificially prepared from gelatin by boiling with dilute acids, and gelatin is a derivative of proteid. Being produced from gelatin, amido-acetic acid received the name glycocoll (gelatin sugar).

Taurin shows its origin from proteid by the amount of sulphur it contains. Kolbe[3] succeeded in producing it synthetically in the following manner: chlorethyl-sulphonate of

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[1] The researches of Adolph Strecker in Liebig's *Annal.* (vol. lxv. p. 130: 1848; vol. lxvii. p. 1: 1848; and vol. lxx. p. 149: 1849) form the groundwork of all subsequent investigations on the bile-acids. Among later works, I must particularly notice a series of experiments carried out by Heinrich Bayer in Hoppe-Seyler's laboratory at Strassburg, "Ueber die Säuren der menschlichen Galle" (*Zeitschr. f. physiol. Chem.*, vol. iii. p. 293: 1879). A summary of the earlier work done in this field is also given here.

[2] Of late years the following authors have worked more particularly on the subject of the constitution of cholalic acid: Tappeiner, *Zeitschr. f. Biolog.*, vol. xii. p. 60: 1876; *Sitzungsber. d. Wiener Akad.*, vol. lxxxvii. part ii.: April, 1878: *Ber. d. deutsch. chem. Ges.*, vol. xii. p. 1627: 1879. Compare also Latschinoff, *Ber. d. deutsch. chem. Ges.*, vol. xii. p. 1518: 1879; vol. xiii. pp. 1052, 1911: 1880; vol. xv. p. 713: 1882; and vol. xviii. p. 3039: 1885; as well as Hammarsten, *Nova Acta Reg. Soc. Scient. Upsala*, ser. iii.: 1881; Kutscheroff, *Ber. d. deutsch. chem. Ges.*, vol. xii. p. 2325: 1879; Clève, *Compt. rend.*, vol. xci. p. 1073: 1880; and *Oefversigt af Kongl Vetenkaps. Akad. förh.*, No. 4, 1882.

[3] Kolbe, *Ann. d. Chem. u. Pharm.*, vol. cxxii. p. 33: 1862.

silver, $C_2H_4ClSO_3Ag$, heated at 100° C. in sealed tubes with a concentrated solution of ammonia, yields silver chlorid and amido-ethyl sulphonic acid, $C_2H_4(NH_2)SO_3H$. This is identical with the taurin obtained from bile.

The comparative amounts of taurocholic and glycocholic acids vary in the bile of different mammals. Glycocholic acid predominates in bullock's bile, whereas the bile of carnivora appears to contain taurocholic acid only; at any rate, this is true of dog's bile.[1] Both acids are found in human bile in very varying proportions, although glycocholic acid always predominates.[2] Jacobsen even found the human bile in one case quite free from sulphur, and in three other cases the sulphur was only contained as a sulphate.[3]

To the specific constituents of bile belong also the bile pigments, of which two occur in the bile of most vertebrates; one red-brown, bilirubin, and the other green, biliverdin. The first is readily converted into the second by oxidation. According to the preponderance of one or the other, and according to the amount of each, the bile is of a yellow, brown, or green color. Both coloring matters have been obtained in a crystalline form. Bilirubin has the composition $C_{32}H_{36}N_4O_6$; biliverdin, $C_{32}H_{36}N_4O_8$.[4] They are closely related to hematin and hemoglobin, and we shall have later on to consider their mode of origin from the latter in greater detail. Both coloring matters behave like acids; they form soluble compounds with metals of the potassium group, insoluble ones with those of the calcium group. Certain gall-stones owe their origin to the formation of these insoluble compounds in the bile-ducts, under conditions which have not yet been sufficiently investigated. The amount of coloring matter in normal bile is always very small. Stadelmann[5] found, for instance, an average of 0.16 grm. of bilirubin in a dog's bile in twenty-four hours.

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[1] Strecker, *Ann. d. Chem. u. Pharm.*, vol. lxx. p. 178: 1849; Hoppe-Seyler, *Journ. f. prakt. Chem.*, vol. lxxxix. p. 283: 1863.

[2] O. Jacobsen, *Ber. d. deutsch. chem. Ges.*, vol. vi. p. 1026: 1873; Trifanowsky, Pflüger's *Arch.*, vol. ix., p. 492: 1874; Socoloff, *ibid.*, vol. xii. p. 54: 1876; Hammarsten, *Upsala Läkareförenings förhandlingar*, vol. xiii. p. 574: 1878; Hoppe-Seyler, "Physiologische Chemie," p. 301: Berlin, 1881. Gerald F. Yeo and E. F. Herroun, *Journ. of Physiol.*, vol. v. p. 116: 1884.

[3] O. Jacobsen, *loc. cit.*, p. 1028.

[4] Städeler, *Vierteljahrschrift der Züricher naturf. Ges.*, vol. viii. p. 1: 1863; *Ann. d. Chem.*, vol. cxxxii. p. 323: 1864; Thudichum, *Journ. f. prakt. Chem.*, vol. civ. p. 193: 1868; Maly, *Journ. f. prakt. Chem.*, vol. civ. p. 28: 1868; or *Sitzungsber. d. Wiener Akad. d. Wissensch.*, vol. lvii. part ii.: 1868; vol. lxx. part iii.: July, 1874; vol. lxxii. part iii.: October, 1875; *Ann. d. Chem. u. Pharm.*, vol. clxxxi. p. 106: 1876.

[5] Ernst Stadelmann, *Arch. f. exper. Path. u. Pharm.*, vol. xv. p. 349: 1882.

These pigments do not appear to be of any importance in intestinal processes.

Besides these specific constituents, the bile always contains soaps, lecithin, and cholesterin (see Lecture VI.). The quantity of the latter is considerable; it may amount to 2½ per cent. It is absolutely insoluble in pure water, and is kept dissolved in the bile by the presence of soaps and bile-salts. Under pathological conditions, of which nothing definite is known, cholesterin separates out in the bile-ducts and forms concretions, which are partly pure and partly mixed with bilirubin and carbonate of lime.

Lastly, mucin belongs to the constant biliary constituents. This is not however a product of the liver-cells, but of the epithelial cells which line the mucous membrane of the larger bile-ducts, and especially of the gall-bladder. The latest and most complete experiments on the chemical qualities of mucin have been carried out by Landwehr.[1] He arrives at the conclusion that mucin is a compound of proteid with a colloid carbohydrate, which latter he designates "animal gum."

[Of late years the mucins and mucoids have been the subjects of several careful investigations, the true starting-point of which may be found in Schmiedeberg's masterly work[2] on the composition of chondrin. He found that chondrin could be regarded as a combination of gelatin with a conjugated sulphuric acid, *viz.*, chondretin-sulphuric acid. Chondretin, itself not a reducing substance, could be converted by boiling with dilute acids into chondrosin, which has a strongly reducing action on cupric hydrate, and can be regarded as a combination of glycosamine ($C_6H_{11}O_5NH_2$) and glycuronic acid ($COOH \cdot C_5H_9O_5$). In chondrin therefore the group which gives rise to the reducing substance on boiling with acids, contains nitrogen. This is also the case with the mucins so far as they have been investigated. Thus Müller[3] obtained pure glycosamine hydrochlorate from mucin of the submaxillary gland. Leathes[4] investigated the mucoid of ovarial cysts. On digestion and treatment in alkaline solution with copper acetate, a gelatinous precipitate is formed which contains the reducing groups of the mucin. The results of analysis gave the formula for this compound $C_{12}H_{21}CuNO_{10} + 2HCl$. The reducing substance therefore has probably the

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[1] H. A. Landwehr, *Zeitschr. f. physiol. Chem.*, vol. viii. pp. 114, 122: 1883; and vol. ix. p. 361: 1885; also *Centralbl. f. d. med. Wissensch.*, p. 369: 1885.

[2] O. Schmiedeberg, *Arch. f. exper. Path. u. Pharm.*, vol. xxviii. p. 355: 1891.

[3] Müller, *Sitzungsber. d. Gesell. z. Beförderung d. ges. Naturwissensch. z. Marburg*, No. 6, p. 117–126: 1898.

[4] J. B. Leathes, *Arch. f. exper. Path. u. Pharm.*, vol. xliii. p. 245: 1899.

formula $C_{12}H_{23}NO_{10}$. Leathes gives it the name of para-mucosin and regards it as possibly a dihexosamine.]

I subjoin the following analyses as instances of the highly variable quantitative composition of human bile:—

OBTAINED FROM THE GALL-BLADDER. FROM A FISTULA.

IN 1000 PARTS OF BILE.	Frerichs.[1]		Gorup-Besanez.[2]		Trifanowsky.[3]		Hoppe-Seyler.[4]	Jacobsen.[5]
	Man eighteen years of age. Cause of death, hanging.	Man twenty-two years of age. Accidental death.	Man forty-nine years of age. Beheaded.	Woman twenty-nine years of age. Beheaded.	Collected from gall-bladders in post-mortems. I.	II.	From dead bodies.	
Water	860.0	859.2	822.7	898.1	908.8	910.8	—	977.4
Solid substances	140.0	140.8	177.3	101.9	91.2	89.2	—	22.6
Mucin	—	—	—	—	24.8	13.0	12.9	2.3
Other substances insoluble in alcohol	26.6	29.8	22.1	14.5	4.6	14.6	1.4	
Sodium taurocholate	102.2	91.4	107.9	56.5	7.5	19.3	8.7	—
Sodium glycocholate					21.0	4.4	30.3	10.1
Sodium palmitate and stearate	—	—	—	—	8.2	16.3	13.9	1.4
Sodium oleate	—	—	—	—				
Fat	3.2	9.2	47.3	30.9	5.2	3.6	7.3	0.10
Lecithin	—	—				0.2	5.3	0.05
Cholesterin	1.6	2.6			2.5	3.4	3.5	0.56
Inorganic salts	6.5	7.7	10.8	6.3	—	—	—	8.5
KCl	—	—	—	—	—	—	—	0.28
NaCl	2.5	2.0	—	—	—	—	—	5.5
Na_2CO_3	—	—	—	—	—	—	—	0.95
Na_3PO_4	2.0	2.5	—	—	—	—	—	1.3
$CaCO_3$	—	—	—	—	—	—	—	—
$Ca(PO_4)_2$	1.8	2.8	—	—	—	—	—	0.37
$Mg_2P_2O_7$			—	—	—	—	—	Trace
$CaSO_4$	0.2	0.4	—	—	—	—	—	—
$FePO_4$	Trace	Trace	—	—	—	—	Trace	Trace

These analyses show that the bile obtained from the gall-bladder is much more concentrated than that obtained from the fistula. It is therefore evident that an absorption of water occurs in the gall-bladder. The analyses of dog's bile by

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[1] Frerichs, *Hannover Ann.*, Jahrg. v. Heft i.: 1845.

[2] Von Gorup-Besanez, *Prager Vierteljahrschr.*, vol. iii. p. 86: 1851.

[3] Trifanowsky, Pflüger's *Arch.*, vol. ix. p. 492: 1874.

[4] Hoppe-Seyler, "Physiologische Chemie," p. 301: Berlin, 1881.

[5] O. Jacobsen, *Ber. d. deutsch. chem. Ges.*, vol. vi. p. 1026: 1873. The bile was taken, at intervals of a few days, from a biliary fistula open for several weeks, the patient being a powerful man.

Hoppe-Seyler,[1] in which he compared the bile found in the bladder, and collected while the animal was fasting, with that from a temporary fistula on the same animal, are in accordance with this observation.

ONE HUNDRED PARTS OF BILE CONTAIN—	Bile from bladder.		Bile from fistula.	
	I.	II.	I.	II.
Mucin	0.454	0.245	0.053	0.170
Alkaline taurocholate	11.959	12.602	3.460	3.402
Cholesterin	0.449	0.133	0.074	0.049
Lecithin	2.692	0.930	0.118	0.121
Fats	2.841	0.083	0.335	0.239
Soaps	3.155	0.104	0.127	0.110
Other organic substances, not soluble in alcohol	0.973	0.274	0.442	0.543
Inorganic substances, not dissolved in alcohol	0.199	—	0.408	—
In the above: K_2SO_4	0.004	—	0.022	—
Na_2SO_4	0.050	—	0.046	—
NaCl[2]	0.015	—	0.185	—
Na_2CO_3	0.005	—	0.056	—
$Ca_32(PO)_4$	0.080	—	0.039	—
$FePO_4$	0.017	—	0.021	—
$CaCO_3$	0.019	—	0.030	—
MgO	0.009	—	0.009	—

More recently Hammarsten[3] has had the opportunity of analyzing a number of specimens of human bile obtained from the gall-bladder as well as from fistulæ.

	Bile from fistula.							From gall-bladder.	
	1	2	3	4	5	6	7	1	2
Solids	1.63	2.06	2.52	2.84	2.45	3.53	2.54	17.03	16.02
Water	98.37	97.94	97.48	97.16	97.55	96.47	97.46	82.97	83.98
Mucin and pigment	0.36	0.28	0.53	0.91	0.88	0.43	0.52	4.19	4.44
Bile-salts	0.26	0.85	0.93	0.81	0.56	1.82	0.90	9.70	8.72
Taurocholate	0.06	0.11	0.30	0.05	—	0.21	0.22	2.74	1.93
Glycocholate	0.20	0.74	0.63	0.76	—	1.61	0.69	6.96	6.79
Fatty acids	0.04	—	0.12	0.02	—	0.14	0.10	1.12	1.06
Cholesterin	0.05	0.08	0.06	0.10	0.06	0.16	0.15	0.99	0.87
Lecithin }	0.02	0.03	0.02	0.05	0.02	0.06	0.07	0.22	0.14
Fat }				0.08		0.10	0.06	0.19	0.15
Soluble salts	0.85	0.80	0.81	0.81	0.89	0.68	0.73	0.29	0.30
Insoluble salts	0.04	0.02	0.03	0.04	0.03	0.05	0.02	0.22	0.24

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[1] Hoppe-Seyler, *loc. cit.*, p. 302.

[2] The greater part of the NaCl was dissolved by alcohol, and not estimated.

[3] Olf Hammarsten, *Nova Acta Reg. Societat. Scient. Upsal.*, ser. iii., vol. 16: 1893.

Having ascertained the composition of the bile, we must now consider its uses. There has been much dispute on this point. Some have even denied that it is of any essential use whatever, and have regarded it simply as an excretion like the urine. The fact that the bile is poured into the commencement of the intestine, into the duodendum, is opposed to this view. If the bile were an excretion, we should expect the bile-duct to open into the lower end of the rectum, just as the ureter opens into the cloaca in the lower vertebrates. It is impossible not to believe that bile, in its long passage through the intestines, must have some serious duties to perform.

The constituents of the bile are, to a very large extent, reabsorbed by the intestine—a fact which is strongly opposed to its being an excretion. The bile acids, which are the most important constituents, are split up by the ferments contained in the intestine into cholalic acid and taurin or glycocoll; the latter, a very easily soluble substance, disappears entirely.[1] Of the cholalic acid only a very small part is excreted in the feces. Concerning the ultimate fate of the taurin nothing is known with certainty.[2]

If the bile were an excretion like urine, we should expect to find the quantity of nitrogen and sulphur in the bile varying proportionately with the amount of proteid decomposed in the body. As a matter of fact, this is not the case. We know from the researches of Kunkel[3] and Spiro,[4] conducted on dogs with biliary fistulæ, that only a small part of the sulphur and nitrogen resulting from proteid metabolism appears in the bile, and that it is but very slightly increased by a larger supply of food. When the amount of proteid allowed the dog was multiplied eightfold the nitrogen and sulphur of the bile were only doubled.

All these facts speak in favor of the view that the bile must be regarded as a secretion, like the other secretions which are poured into the alimentary canal and exert a manifestly important influence in the process of digestion. But the following fact shows that the bile occupies a peculiar position. The secretion of the bile begins in the third month of embryonic

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[1] On the further fate of the glycocoll, see Lecture XIX.

[2] The most extended researches on taurin have been made by Salkowski, *Ber. d. deutsch. chem. Ges.*, vol. v. Heft. xiii.: 1872; vol. vi. pp. 744, 1191, 1312: 1873; Virchow's *Arch.*, vol. lviii. p. 460: 1873.

[3] Kunkel, "Unt. über den Stoffwechsel in der Leber": Würzburg, 1875: *Ber. d. säch. Ges. d. Wissensch.:* November, 1875; Pflüger's *Arch.*, vol. xiv. p. 344: 1876.

[4] Spiro, Du Bois' *Arch.*, Suppl., p. 50: 1880 (from Ludwig's laboratory in Leipzig).

life; the activity of all the other glands which empty their secretions into the alimentary canal does not commence till after birth, when food is first taken.[1] Moreover the observation of Lukjanow[2] that the secretion of bile in guinea-pigs is only slightly diminished during starvation is against the conception of bile as a digestive secretion.

It has been attempted to decide the question as to the function of the bile in intestinal processes by watching the digestive disturbances which occur when the bile is withdrawn.[3] It appears that dogs with a biliary fistula digest proteid and carbohydrates as completely as healthy dogs. They can be adequately fed on lean meat and bread. Fat is the only food-stuff that they cannot entirely digest, and a considerable part of it—more than half if much be eaten—reappears in the feces, which for this reason are of a light gray or white color. This is not owing to the want of the bile pigments, as was originally thought. The black color of the normal feces after meat diet is not caused by the bile pigments, but by hematin and sulphid of iron. If the light gray feces of an animal with a biliary fistula or of a jaundiced person be extracted with ether, which dissolves the fat, the dark color is again evident. In consequence of the imperfect absorption of the fat, the other food-substances cannot be completely digested. The fat encloses the proteids, which become decomposed by the putrefactive organisms of the intestine. This explains the putrefactive smell of the feces and the intestinal gases in dogs with a biliary fistula. The breath of the animals becomes fetid. These symptoms are all absent when a diet without fat is given.

Many of the dogs with a biliary fistula that have been under observation became very thin, and a few died with every symptom of starvation. This is readily comprehensible if we consider how high the heat-equivalent of fats is, and how

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[1] Zweifel, "Unt. über den Verdauungsapparat des Neugeborenen": Berlin, 1874. An account of the comprehensive literature on the action of the digestive glands in embryonic life is to be found in W. Preyer's "Specielle Physiol. des Embryo," p. 306: Leipzig, 1885.

[2] S. M. Lukjanow, *Zeitschr. f. physiolog. Chem.*, vol. xvi. p. 87: 1891.

[3] Schwann, *Arch. f. Anat. u. Physiol.*, p. 127: 1844; Blondlot, "Essai sur les fonctions du foie et de ses annexes": Paris, 1846; Bidder and Schmidt, *loc. cit.;* Köllicker and Müller, *Verh. d. phys. med. Ges. zu Würzburg*, vol. v. p. 232: 1854; vol. vi.: 1855; Arnold, "Zur Physiol. der Galle," Denkschrift für Tiedemann: Mannheim, 1854; and "Die physiol. Anstalt der Universität Heidelberg": 1858; C. Voit, Beitr. zur Biolog. Festgabe Th. Bischoff zum Doctorjubiläum, Stuttgart, p. 104; F. Röhmann, Pflüger's *Arch.*, vol. xxix. p. 509: 1882. The observations on icteric patients are in complete harmony with those on dogs with biliary fistulæ. In this connection see Fr. Müller, *Sitzungsber. der physikal. med. Ges. zu Würzburg*, No. 7: 1885.

difficult it is to replace this potent source of energy by other articles of food. It is necessary for this purpose to consume very large quantities of proteid and carbohydrates, and the digestion of these substances is disturbed by the presence of the unabsorbed fat. Therefore only those dogs kept their weight which were fed on food as far as possible free from fat, and that in very large quantities.

It is therefore an undoubted fact that bile aids in the absorption of fat. This power is partly explained by the emulsifying action on fats already mentioned (p. 164), which the bile possesses in common with the pancreatic and intestinal juices. In agreement with this is the fact that the withdrawal of the bile only diminishes the absorption of fat, and does not completely stop it. Possibly it is not only the emulsifying action of the bile which assists in the absorption of fat. Wistinghausen[1] showed that, when oil is separated from a watery fluid containing bile in solution by an animal membrane soaked in bile, it filters through without any pressure, whereas it can only be made to pass through a membrane soaked in water by the employment of high pressure. But the intestinal wall does not behave like a dead membrane. Thanhoffer,[2] who first observed in the frog's intestine the active functions of the epithelial cells in the absorption of fats, also mentions that the movement of the protoplasmic processes becomes more active when the epithelial cells are moistened with bile.

The process of fat absorption is however by no means explained by the facts we have discussed. The emulsion of the fat by the alkaline constituents of the intestinal pancreatic juices and of the bile will not serve alone to explain the process. The pancreatic secretion and bile have still another part to play in the process. We know for certain that the absorption can only take place by the coöperation of both juices. In the rabbit the pancreatic duct opens into the duodenum 10 cms. lower down than the bile duct. After the administration of fatty food the lacteals may be seen to be transparent in the interval between these two openings, and only assume the milky appearance below the orifice of the pancreatic duct. Dastre experimentally changed the relative position of the two ducts. He ligatured the common bile duct and made a fresh opening for the bile by a communication

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[1] Wistinghausen, "Experimenta quædam endosmotica de bilis in absorptione adipum neutralium partibus," Dissert.: Dorpat, 1851. A translation of this dissertation was published by J. Steiner in Du Bois' *Arch.*, p. 137 : 1873.

[2] Ludwig von Thanhoffer, Pflüger's *Arch.*, vol. viii. p. 40 1874.

between the gall-bladder and the small intestine some distance below the opening of the pancreatic duct. After this procedure the milky appearance of the lacteals first became evident below the point of entry of the bile. We must therefore conclude that neither the bile by itself, nor the pancreatic juice by itself, can effect any considerable absorption of fat.

[It seems most probable that the absorption of fat resembles that of the other food-stuffs in that it takes place in a state of solution. The pancreatic juice first causes a splitting of the fat into fatty acid and glycerin. If the reaction is alkaline the fatty acid may combine with the alkalies to form soaps. Whatever be the reaction of the intestinal contents, however, the fat is absorbed either as a solution of fatty acids in the bile-salts or as a solution of soaps in the bile. The coöperation of both juices is therefore necessary: the pancreatic juice to split the fats, the bile to dissolve the products of this fermentative action and carry them into solution into the epithelial cells of the intestine, where the fatty acids and soaps are resynthesized with glycerin to form neutral fats, while the bile-salts are carried by the portal blood to the liver to be turned out again into the beginning of the intestinal tract and serve as a vehicle for a still further quantity of fat.]

No action of bile on proteïd could be demonstrated in experiments on artificial digestion. A slight diastatic effect was indeed noticed, but, for the reasons above stated no weight can be attached to this observation. Bile must however have some other functions besides that of assisting in fat absorption, since the quantity of bile secreted by herbivora, whose diet is poor in fat, is much greater than that formed by carnivora with their rich fatty diet.

An antiseptic property has also been ascribed to bile on account of the putrefactive phenomena, mentioned above, which appeared in the intestine of animals with a biliary fistula. But, as was then shown, these signs of putrefaction are capable of another explanation; they depend only indirectly upon the absence of the bile. For as the bile cannot protect even itself from putrefaction, it is evident that it can have but little antiseptic power. Any one who has experimented with bile knows that it emits a strong putrefactive odor after a few days, even when kept at the temperature of a dwelling-room. The doctrine of the antiseptic properties of bile has recently again found supporters in Maly and Emich.[1] They affirm that the bile acids, and especially taurocholic acid, prevent the development of putrefactive organisms, and that taurocholic acid in

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[1] Maly and Fr. Emich, *Monatshefte f. Chem.*, vol. iv. p. 89: 1883.

many cases is nearly as powerful as salicylic acid and phenol. This view has been confirmed by Lindberger[1] as well as by Gley and Lambling.[2] But still it is only the free bile acids that hinder putrefaction, and not the salts. This explains why bile itself which is alkaline or neutral, rapidly decomposes outside the body, whereas the bile acids can develop their antiseptic properties only in the upper portion of the small intestine, where an acid reaction prevails.

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[1] V. Lindberger, *Bulletin de la Soc. imp. des naturalistes de Moscou:* 1884.

[2] Gley and Lambling, *Rev. biol. du Nord de la France*, vol. i.: 1888.

LECTURE XIII

THE PATHS OF ABSORPTION, AND THE IMMEDIATE DESTINATION OF THE ABSORBED FOOD-STUFFS

WE have hitherto been considering the fate of the food-substances in the intestine and the preparation they undergo previous to absorption. Our attention must now be given to the paths which the food-stuffs follow in undergoing absorption.

The investigations of Ludwig and of his pupils Röhrig,[1] Zawilski,[2] von Mering,[3] and Schmidt-Mülheim,[4] have thrown an unexpected light on this subject. Till modern times it was commonly assumed that the main stream of nutriment passed from the intestine through the thoracic duct. But Ludwig's experiments have shown that it is only the fats which take this path. The whole stream of watery solutions, carbohydrates, proteids, salts, etc., proceeds from the intestine to the heart, through the portal system and the liver. The watery solutions penetrate the walls of the capillaries which form a network on the internal surface of the intestine, and enter the blood direct. The droplets of fat alone are brought to the commencement of the lacteals by the active movements of the epithelial cells.

If, in a living dog, the spot where the thoracic duct opens into the jugular vein[5] be laid bare, a cannula may be introduced into the duct, and the amount of chyle that flows out in a given time estimated. The astonishing fact was discovered that the amount was no greater during digestion than in a fasting animal.[6] The sole difference was that the fluid was transparent in the case of fasting animals, whereas after food

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[1] A. Röhrig, *Ber. d. sächs. Ges. d. Wissensch. Math. phys. Classe*, vol. xxvi.: 1874.

[2] Zawilski, *Arbeiten aus der physiol. Anstalt zu Leipzig*, p. 147: 1876.

[3] von Mering, Du Bois' *Arch.*, p. 379: 1877.

[4] A. Schmidt-Mülheim, *ibid.*, p. 549.

[5] For the mode of operation and the precautions adopted during the subsequent post-mortem, see A. Röhrig, *loc. cit.*, pp. 12, 13; and Schmidt-Mülheim, *loc. cit.*, pp. 559–561.

[6] Zawilski, *loc. cit.*, pp. 161, 162.

it was white and opaque from the presence of minute particles of fat.

On the other hand, the amount of SUGAR in the chyle was not found to be greater during the digestion of starch and sugar than in the fasting animal—0.1 to 0.2 per cent.[1] The amount of sugar in the chyle was always the same as in the lymph from the cervical lymphatic trunks, and in the serum[2] of the arterial blood. The sugar of the chyle had therefore passed through the walls of the intestinal capillaries into the chyle-vessels along with the blood-plasma. From the intestine no sugar had got through into the chyle.

Three hundred and fifty cubic centimeters of chyle, containing only 0.45 grm. of sugar, flowed during the space of four and a half hours from the thoracic duct of a dog, after it had eaten 100 grms. of grape-sugar and 100 grms. of starch.[3]

We must therefore conclude that the sugar reaches the capillaries and the portal system direct from the intestine. But now we see that the amount of sugar in the blood is not increased even after a meal rich in carbohydrates. An adult man has about 5 liters of blood, and in each liter 0.5 to 1.5 grms. sugar, rarely more than 2 grms., so that the whole blood contains at most 10 grms. This amount remains the same in a hungry as in a well-fed animal. During the few hours elapsing after a meal rich in carbohydrates, as much as 400 grms. of sugar may pass into the blood. What becomes of this sugar? It cannot always be employed as a source of energy as quickly as it is absorbed, especially when the body is at rest and does not need to produce much heat. The sugar must therefore be stored up somewhere and in some form or other, in order that it may serve as a store of potential energy for later utilization.

We naturally think first of glycogen, the colloid carbohydrate stored up in the liver and muscles, which we shall have to deal with more fully later on. We know that this store of glycogen gradually disappears in hunger and during work (compare Lectures XXII. and XXIII.), and rapidly increases in amount after ingestion of carbohydrates.

But the large quantities of sugar which are frequently absorbed from the intestine into the blood within a short space of time cannot possibly be all stored up as glycogen. The

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[1] von Mering, *loc. cit.*, pp. 382–384, 398.

[2] The blood-corpuscles contain no sugar, or only a trace of it (see von Mering, *loc. cit.*, p. 382; and A. M. Bleile, Du Bois' *Arch.*, p. 62: 1879).

[3] von Mering, *loc. cit.*, p. 398.

total amount of glycogen in the liver in man never exceeds 150 grms., and a similar quantity might be stored up in the whole mass of muscles. This store however is by no means used up at the time when fresh carbohydrates are taken into the body, and disappears only after several weeks' starvation. If therefore 400 grms. of sugar are poured into the blood within a few hours after a carbohydrate meal, it is evident that only a small proportion of it can be laid down as glycogen; and we must assume that the greater part of it is converted into fat. In this form very large quantities of food can be stored up in the connective tissue of all the organs, and we shall see later (Lecture XXIV.) that carbohydrates are, as a matter of fact, converted into fat in our tissues.

The present state of our knowledge enables us therefore to form the following conception concerning the fate of the sugar that is taken into our body:—Sugar is an important food-stuff—an important source of energy for the muscles and probably for all contractile tissues. Hence provision has been made in our bodies for a certain percentage of it to be constantly present in the blood which circulates through all the tissues. If its amount in the blood increases to more than 3 per mille, excretion of sugar takes place through the kidneys (compare Lecture XXVI.). This loss of precious food-stuff is prevented by the fact that the liver and muscles at once store up as glycogen any excess above the normal resulting from a rapid absorption. If the consumption be increased by work and heat production so as to diminish the normal percentage of sugar in the blood, the muscles and liver at once give back a portion of the glycogen to the blood in the form of sugar. If the store of glycogen is insufficient, fat is converted into sugar and transferred to the blood. In a subsequent lecture (Lecture XXII.) we shall deal with the grounds for assuming that such a conversion takes place. We know for a fact that, after long-continued hunger, when the store of glycogen has quite disappeared, the percentage of sugar in the blood remains constant. Sugar is also in all probability formed from proteid (compare Lecture XXII.).

The question now arises as to the reason why the amount of FAT in the blood is not regulated in the same way? The stream of fat being poured freely into the innominate vein goes almost directly to the heart. May not this be fraught with danger? The blood is in fact frequently flooded by the stream of fat. If blood, which has been taken from a dog a few hours after a meal containing an abundance of fat, be defibrinated, the serum separated out after the blood-corpuscles have sunk, appears as white as milk, occasionally with a regular cream-like layer on the top. This abundance of fat in the blood is quite harmless, because the fat-droplets are so small that they circulate without hindrance through the capillaries. The fat gradually disappears from the blood, for the obvious reason that it travels through the walls of the capillaries, and becomes stored up in the cells of the connective tissue (compare Lecture XXIV.). It is impossible for the fat to be decomposed within the vessels, since, as we know, processes of oxidation never take place in the blood (see Lecture XVII.).

The fat which reaches the blood under abnormal conditions behaves very differently. In comminuted fractures of the bones causing a destruction of the marrow which contains a great deal of fat, or when the soft parts containing much fat are damaged in any way, fat-droplets are often drawn into the lymph-vessels and carried with the lymph into the blood. If the amount of fat is considerable, the larger particles of fat block the pulmonary capillaries over wide areas, edema of the lungs is set up, and it occasionally happens that the patient dies with all the signs of increasing dyspnea. The fat may in these cases seek a way out through the kidneys, and the occurrence of droplets of fat in the urine after fractures of bone is not at all uncommon.

The question might now be raised as to why this fat, which reaches the blood from the tissues, is not emulsified into minute droplets, seeing that the blood contains sodium carbonate and other basic alkaline salts. The answer is to be found in the fact already mentioned (p. 164), that sodium carbonate can only emulsify fat which has a little free fatty acid mixed with it, and not neutral glycerids such as fresh fats are. But no fat can be fresher than when it comes straight from the living tissues into the current of blood.

It has not yet been decided whether all fat passes from the intestine into the lacteals, or whether a part enters the blood directly through the walls of the capillaries of the intestinal villi. Even if a portion does take the latter path, it appears to be inconsiderable. Zawilsky found very little fat in the blood of a dog, which had been fed on a highly fatty diet, and whose chyle was drawn off. If fat passed into the capillaries of the intestinal villi to any extent, we should expect to find that an abundant diet of fat would be followed by a perceptibly larger increase in the portal than in the arterial blood. Comparative estimates, made in Heidenhain's laboratory, showed that there was the same amount of fat in both kinds of blood.[1] An average of five analyses of blood from the same number of dogs gave—

	Dry residue.	Amount of fat in total blood.	Amount of fat in dry residue.
Carotid	22.34 per cent.	0.86 per cent.	3.65 per cent.
Portal vein	22.84 "	0.85 "	3.35 "

The only question that remains for us to consider refers to the path the PROTEIDS take in order to become absorbed. There are special difficulties to contend against in experiments on this subject, because proteids already form the chief constituents of blood and lymph. If we consider how large is the amount of blood which passes through the intestinal capillaries, we cannot expect to be able to trace an increase of proteid in the blood in consequence of intestinal absorption. Ludwig and Schmidt-Mülheim therefore adopted another method. They tied the thoracic duct, and found that this did not in any way prevent the absorption of the proteid, and that therefore the proteid takes the other path, through the portal vein. I will here quote one of these experiments.[2]

Weight of dog, 14.73 kgrms. The dog, which had previously fasted for four days, passed all his urine before the operation. The jugular and subclavian veins and lymphatic ducts on both sides were now tied. An hour after the operation, and again on the following afternoon, the dog ate on each occasion 400 grms. of meat; and the whole time was in excellent condition. Forty-eight hours after the operation, the animal was killed by opening the carotid. On post-mortem examination, the chyle was found completely shut off from the blood-vessels. The alimentary canal contained 7.37 grms. N. It thus appears that 583.24 grms. of meat were absorbed after complete interruption of the chyle-current. The urine secreted after the operation contained 21.95 N, an amount corresponding to the food absorbed.

Four other experiments carried out in the same manner gave the same result. We thus see that proteid, like all food-substances dissolved in water, enters the blood directly through the walls of the intestinal capillaries.

The question now arises, whether all proteid, in order to be able to follow this path, must be peptonized beforehand, or whether a portion of the proteid is absorbed as such.

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[1] Heidenhain, Pflüger's *Arch.*, vol. xli. Sup., p. 95: 1888.

[2] Schmidt-Mülheim, *loc. cit.*, p. 565, Exp. 5.

There is no *à priori* ground for supposing that proteid is not absorbed unchanged. If fat-droplets, visible under the microscope, and even entire leucocytes, can leave the blood-capillaries and travel through the tissues, why may not a proteid molecule find its way through the capillary wall? Voit and Bauer have endeavored to prove this experimentally.[1] A coil of small intestine of a live dog or cat was cleansed of all contents, and a piece of a certain length was tied at both ends with a double ligature; a solution of proteid was then injected into this ligatured piece, the coil replaced, and the abdominal wound closed. The percentage of proteid contained in the solution being known, the operators estimated the quantity injected by the loss of weight of the syringe used. After a few hours the animal was killed, and the amount of proteid in the piece of intestine was estimated. It was invariably found that a considerable portion had disappeared in from one to four hours—from 16 to 33 per cent. of egg-albumin, from 28 to 95 per cent. of acid-albumin prepared from muscle. Voit and Bauer refute the obvious objection that the coil of small intestine was not thoroughly cleansed from the peptic and pancreatic ferments, as they found that the remainder of the proteid in the piece that had been tied was always completely coagulable by boiling. No peptone was present with the proteid.

Voit and Bauer have also injected solutions of proteid into the rectum of fasting dogs, and determined the absorption of the unchanged proteid from the increased secretion of urea. Eichhorst[2] draws the same conclusion from similar experiments. These experiments are open to the objection that the pancreatic ferment may extend into the rectum. The experiments of Czerny and Latschenberger,[3] however, are free from this objection, because they were made on a man with an artificial anus at the sigmoid flexure. The rectum could be syringed quite clean through the fistula. If a solution of proteid were then injected, and the rectum again washed out after from twenty-three to twenty-nine hours, it was found that from 60 to 70 per cent. of the proteid had disappeared. Nencki[4] and his pupils came to the same conclusion as the result of a similar experiment on man.

A few authors have gone so far as to maintain that only

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[1] C. Voit and J. Bauer, *Zeitschr. f. Biolog.*, vol. v. p. 562: 1869.

[2] Hermann Eichhorst, Pflüger's *Arch.*, vol. iv. p. 570: 1871.

[3] V. Czerny and J. Latschenberger, Virchow's *Arch.*, vol. lix. p. 161: 1874.

[4] MacFadyen, Nencki and Sieber, *Arch. f. exper. Path. u. Pharm.*, vol. xxviii. p. 344: 1891.

the unaltered proteid is of any use after absorption in replacing the proteid used up in the tissue, and that the peptones, on the contrary, undergo rapid further decomposition, and only serve as sources of energy.

Certain facts seem to agree with this view. A fasting animal is very economical with its store of proteid, and its excretion of urea is very limited; whereas, after a meal consisting largely of proteids, an amount of nitrogen closely corresponding to the proteid eaten reappears in the urine in the course of the next twelve hours. It might *à priori* be expected that the nitrogenous equilibrium would be maintained if a fasting dog were to eat as much proteid as corresponds to the nitrogen excreted in hunger, together with plenty of non-nitrogenous food. It might be thought that it would be indifferent whether the necessary proteid were derived from the food, or from the animal's own tissues. But it is not so. If a fasting dog be given only as much proteid as corresponds to the proteid used up in fasting, it still goes on consuming the nitrogenous constituents of its own tissues. Nitrogenous equilibrium, *i. e.*, the condition in which the animal excretes no more nitrogen than he takes in, is not established until three times as much proteid is given.[1]

Ludwig and Tschiriew[2] injected into the vein of a dog defibrinated blood from another dog. This caused only an inconsiderable increase of nitrogenous excretion. But if they gave the dog the same quantity of blood by the mouth, the excretion of nitrogen rose proportionately to the amount given. Forster[3] attained the same result in similar experiments. [Pflüger however has shown that the assimilation of serum is as complete when it is administered intravenously as when it is given by the mouth.]

Proteid therefore behaves very differently according to the way in which it reaches the blood and the tissues. When taken up from the intestine, it rapidly undergoes a destructive metabolism.

This fact was quoted in support of the theory that peptones are not assimilable. It was claimed that proteids absorbed from the intestine, being mostly peptonized, must therefore go on decomposing rapidly; and, further, that only that portion of the proteid which is absorbed as such can be used in building up the tissues.

But the facts are capable of another interpretation, for we

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[1] Voit, *Zeitschr. f. Biolog.*, vol. iii. pp. 29, 30 : 1867.

[2] S. Tschiriew, *Arbeiten aus dem physiol. Institut zu Leipzig*, p. 441 : 1874.

[3] J. Forster, *Zeitschr. f. Biolog.*, vol. ii. p. 496 : 1875.

now know that the peptones are, after absorption, regenerated into proteid. The following experiments show this to be the case.

Plosz[1] fed a dog ten weeks old for eighteen days on an artificial milk, in which the casein and the proteids were replaced by peptones. The animal kept its health on this diet, and its weight increased from 1335 to 1836 grms., or 37.5 per cent. It is very improbable that the weight could increase so much without a corresponding growth of the tissues containing proteid, which must therefore have been formed from the peptones of the food.

Plosz and Gyergyai[2] made a second experiment on a full-grown dog. The animal was fed for six days on an artificial mixture, containing peptone instead of proteid. During this time the weight increased somewhat, and the excretion of nitrogen was a little less than that taken in. This experiment, again, can only be interpreted to mean that proteid had been formed from the peptones.

The proteid stored in the animal tissues may come from two sources: from that which has been absorbed unaltered, and from that formed by the regeneration of the peptones. But what quantitative proportion do they bear to each other? How large is the portion of the proteid of the food which is peptonized in the intestine? Schmidt-Mülheim[3] tried to find an answer to this in the following manner. He fed six dogs on boiled meat, killed them one, two, four, six, nine, and twelve hours after the meal, and examined the contents of stomach and intestine. In each case he found considerably more peptone than dissolved proteid, both in stomach and intestine. It thus appears that the greater part of the proteid became absorbed after peptonization.

What is the fate of peptones after absorption? They are either not found at all or only in very small amount in the blood of digesting animals. Schmidt-Mülheim gives the maximum as 0.028 per cent. of serum; Hofmeister found that it amounted to as much as 0.055 per cent. of the total blood. Peptones are not found in the blood of fasting animals.[4] As might be expected, they cannot be detected in chyle, not even

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P. Plosz, Pflüger's *Arch.*, vol. ix. p. 323 : 1874. Compare Maly, *ibid.*, vol. ix. p. 609 : 1874.

[2] P. Plosz and A. Gyergyai, *ibid.*, vol. x. p. 545 : 1875.

[3] Schmidt-Mülheim, Du Bois' *Arch.*, p. 43 : 1879.

[4] *Ibid.*, pp. 38–42 : 1880; Hofmeister, *Zeitschr. f. physiol. Chem.*, vol. v. p. 149 : 1881; and vol. vi. p. 60, *et seq.* [The small amounts of peptone found by these observers are due to errors of analysis. The blood of healthy animals, whether fasting or fed, never contains the slightest traces of proteoses or peptones.]

when they are found in the blood.[1] If peptone be injected into the blood, it passes into the urine,[2] and none can be traced in the blood after from ten to sixteen minutes.[3] Hofmeister has shown also, that after subcutaneous injection the greater part of the peptone—as much as 72 per cent.—reappears in the urine.[4]

As normal urine never contains peptone, the peptone absorbed from the intestine must be prevented by some means or other from passing into this secretion. The larger portion does not apparently enter the general circulation as peptone, but is previously converted into proteid. But where does this regeneration of peptone to proteid take place? Is it in the liver? If the peptones are considered as decomposition-products from proteid, then the formation of proteid from peptone would be analogous to the formation of glycogen from sugar in the liver. But the portal blood either contains no peptone, or not more than arterial blood.[5]

The only remaining supposition is that the conversion of peptones into proteid takes place mostly within the intestinal walls. The facts observed by Hofmeister are in harmony with this view. He most carefully examined the viscera of dogs while digesting, and found that the stomach and intestinal wall are the only parts of the body in which a supply of peptone is always found during digestion. In most cases small quantities of peptones were also found in the blood, and in four out of ten cases in the spleen. No peptone was ever detected in any other organs or tissues.[6] Hofmeister has also shown that the peptones are always stored in the mucous membrane, and never in the muscular walls of the alimentary canal.[7]

Lastly, Hofmeister has discovered the important fact that peptone soon undergoes a change in the gastric and intestinal wall.[8] The stomach of an animal, immediately after it had been killed, was divided into two symmetrical halves by incisions in the large and small curvatures, or else a piece of in-

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[1] Schmidt-Mülheim, Du Bois' *Arch.*, p. 41 : 1880; Hofmeister, *Arch. f. exper. Path. u. Pharm.*, vol. xix. p. 17 : 1885.

[2] P. Plosz and A. Gyergyai, Pflüger's *Arch.*, vol. x. p. 552 : 1875; Fr. Hofmeister, *Zeitschr. f. physiol. Chem.*, vol. v. p. 131 : 1881.

[3] Schmidt-Mülheim, Du Bois' *Arch.*, pp. 46–48 : 1880; Fano, *ibid.*, p. 281 : 1881. [By the employment of trichloracetic acid as a precipitant for the proteids, it is possible to detect the presence of peptone in blood for as much as two hours after its injection into a vein.]

[4] Fr. Hofmeister, *Zeitschr. f. physiol. Chem.*, vol. v. pp. 132–137 : 1881.

[5] Schmidt-Mülheim, Du Bois' *Arch.*, p. 43 : 1880.

[6] Hofmeister, *Zeitschr. f. physiol. Chem.*, vol. vi. p. 51 : 1882.

[7] Hofmeister, *Arch. f. exper. Path. u. Pharm.*, vol. xix. p. 9 : 1885.

[8] Hofmeister, *Zeitschr. f. physiol. Chem.*, vol. vi. pp. 69–73; and *Arch. f. exper. Path. u. Pharm.*, vol. xix. pp. 8–15 : 1885.

testine was separated by two incisions lengthwise into two equal portions. The mucous membrane was washed with a dilute solution of common salt, one half was thrown at once into boiling water, whereas the other one was previously put for a little time into a moist chamber at 40° C. Far more peptone was always found in the first half than in the second. If the second half were not placed in the boiling water for two or three hours, no peptone was ever found in it. It is for teleological reasons very improbable that the peptone is further split up in the mucous membrane. One can only suppose that the peptone is reconverted into proteid in the mucous membrane of the digestive canal. That it is a vital process is rendered probable from a fact observed by Hofmeister. If one half of the stomach were thrown at once into boiling water, and the other kept in water at 60° C. for a few minutes before being placed for two hours in a temperature of 40° C., the amount of peptone proved to be the same in both halves. A temperature of 60° C. has been found by experience to destroy living animal cells, but not all unorganized ferments. The conversion of peptone into proteid must therefore be brought about by the vital functions of the surviving cells of the extirpated stomach.

The following observation, made by Salvioli[1] in Ludwig's laboratory in Leipzig, perfectly agrees with these results of Hofmeister's. A coil of small intestine, with the piece ot mesentery attached, was cut out of a dog that had just been killed. One gramme of peptone in 10 c.cms. solution was placed in the piece of intestine and the ends closed. Then, after tying the collateral vessels, a current of warm defibrinated blood, diluted with a solution of common salt, was directed into a branch of the mesenteric artery and allowed to flow out again by the corresponding vein. Whilst the blood circulated, the intestine showed marked peristalsis. After the current had lasted four hours, the intestinal contents were examined and were found to consist of about half a gramme of coagulable proteid, with mere traces of peptone. Nor was there any peptone in the blood that had made the circuit. But if peptone were added to the blood beforehand, it was always found unaltered at the end of the experiment. The peptone therefore disappears in the intestinal wall on the way from the intestinal contents into the blood.

I must now return to an observation on the behavior of peptones, and discuss it in somewhat greater detail. We have seen that the reconversion of peptones into proteid within the

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[1] Gaetano Salvioli, Du Bois' *Arch.*, Sup., p. 112: 1880.

intestinal wall is usually not very complete; a part of the peptone generally passes, unchanged by digestion, into the blood. Now, what is the further fate and the significance of this portion? Why does it not pass into the urine, considering that the peptone artificially introduced into the blood does so at once? Hofmeister[1] remarked this fact, for he calculated that the amount of peptone which reached the blood after subcutaneous injection, and passed into the urine, was much less than the quantity that was found in the blood of animals while digesting and which did not pass into the urine. Thus the peptone that has entered the blood from the intestine behaves differently from that which reaches it in any other way. Hofmeister explains this fact by saying that the peptone which has reached the blood from the intestine is not contained in the plasma but in the lymph-cells. The reasons which cause him to adopt this view are as follows:

1. Considerable quantities of peptone are found in pus, and, moreover, principally or even exclusively in the pus-cells, which are identical with the lymph-cells and the colorless blood-corpuscles or leucocytes.[2]

2. When the blood of an animal was examined during digestion, the serum was free from peptone; whereas the uppermost layer of the blood-clot, which always exhibits most leucocytes (compare Lecture XIV.), was found to contain 0.09 per cent. of peptone.[3]

3. The percentage of peptone in the spleen, which is well known to contain leucocytes in abundance, was always found to be higher than that in the blood of the same animal.

4. The adenoid tissue, which contains a moderate number of lymph-cells in famishing and hungry dogs, is literally overflowing with them in the case of well-fed dogs.[4]

5. The cells in the adenoid tissue of animals while digesting show more nuclei undergoing karyokinesis than those of fasting animals.[5]

Finally, Hofmeister's pupil, J. Pohl,[6] has shown that the

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[1] Hofmeister, *Zeitschr. f. physiol. Chem.*, vol. v. p. 148: 1881.

[2] *Ibid.*, vol. iv. p. 274, *et seq.*: 1880.

[3] *Ibid.*, vol. vi. p. 67: 1882.

[4] *Ibid.*, vol. v. p. 150: 1881.

[5] Hofmeister, *Arch. f. exper. Path. u. Pharm.*, vol. xix. p. 32: 1885. Compare also vol. xx. pp. 291–305: 1885; and vol. xxii. p. 306: 1887. [These observations of Hofmeister's possess now little more than historic interest, as the peptone he discovered in the blood was certainly produced during his manipulations for the purposes of analysis. The peptone found in the spleen has been shown lately by Hedin to be due to the presence in the cells of this organ of a special proteolytic ferment, which resembles trypsin in the products of its action, but requires an acid medium.]

[6] Julius Pohl, *ibid.*, vol. xxv. p. 31: 1888.

number of leucocytes in the blood increases during the digestion of food rich in proteid, but not during the absorption of carbohydrates, fats, salts, and water. Pohl has also shown that this increase of leucocytes proceeds from the intestinal wall, for there was always a much larger number in the intestinal veins than in the corresponding arteries.

Thus it appears that the lymph-cells serve not only as the means of transport for the peptones in the blood-current; their increase and growth seem to be intimately connected with the absorption and assimilation of nitrogenous food. As the number of leucocytes in our body is always the same, it follows that, as the proteid becomes absorbed and new cells are produced by division, a corresponding amount of old lymph-cells must die off and decay. This perhaps partially explains the above-mentioned fact, that the absorption of large quantities of proteid is followed by rapid destruction of a corresponding amount of proteid.

At the same time, we are not bound to assume that all the peptone which disappears in the intestinal wall is reconverted into proteid in the lymph-cells of the adenoid tissue, and that this reconversion takes place only through the assimilation, growth, and division of lymph-cells. Heidenhain[1] has called attention to the fact that the nuclei undergoing karyokinesis in the lymph-cells of adenoid tissue are not sufficiently numerous to justify such a conclusion. He considers that the reconversion of the peptones into proteid may occur to a large extent in the epithelial cells, which then surrender it to the blood-plasma of the capillaries forming a network around the intestinal villi, immediately below the epithelial cells.

We must now consider what happens to the peptone which has reached the blood from the intestine. As already mentioned, it very soon disappears from the blood, without passing into the urine. Where does it undergo a change? The conversion does not take place in the blood itself. Hofmeister[2] took two samples of blood from the carotid of a dog during the process of digestion. The first was immediately tested for peptone; the second was kept for two and a half hours at 37° C. before being tested. The amount of peptone was found to be exactly the same in both cases. Hofmeister also laid bare to the utmost extent the carotid and crural arteries of a living dog, applying ligatures above and below as well as to the lateral branches. After half an hour the pieces of artery which had been tied were taken out and their contents removed.

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[1] Heidenhain, Pflüger's *Arch.*, Suppl., vol. xli. pp. 72–74 : 1888.

[2] Hofmeister, *Arch. f. exper. Path. u. Pharm.*, vol. xix. p. 23 : 1885.

Peptone was found in them. It does not therefore disappear in the blood, and must consequently pass into the tissues from the capillaries.[1] [It can, in fact, be detected in the lymph flowing from the thoracic duct within half a minute of its injection into the blood-stream.]

Armed with this knowledge concerning the behavior of peptones in the body, we are now in a position to explain the hitherto enigmatic appearance of peptone in the urine in certain forms of disease. We have seen that the peptones pass into the urine as soon as they reach the blood by some other means than from the intestine. This is obviously the case in all those pathological processes in which peptonuria occurs. Probably in all such cases there is a pathological disintegration of necrotic tissue, as the result of which peptone is formed and is absorbed into the blood;[2] as for instance in those diseases in which there is a considerable accumulation and decomposition of pus—in empyema, purulent peritonitis, pyelitis, in some cases of phthisis with large cavities, and the like. The appearance of peptone in the urine in the stage of resolution of croupous pneumonia may be explained in a similar manner: the peptone reaches the blood when the exudation in the lung is absorbed. As a matter of fact, Hofmeister was able to demonstrate the presence of a considerable quantity of peptone in the infiltrated pneumatic lung.

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[1] Hofmeister, *Arch. f. exper. Path. u. Pharm.*, vol. xix. p. 30 : 1885.

[2] E. Maixner, *Prager Viertelj.*, vol. cxliii. p. 75 : 1879; Hofmeister, *Zeitschr. f. physiol. Chem.*, vol. iv. p. 265 : 1880; R. von Jaksch, *Zeitschr. f. klin. Med.*, vol. vi. p. 413 : 1883; H. Pacanowski, *ibid.*, vol. ix. p. 429 : 1885.

LECTURE XIV

THE BLOOD

Having followed the course of the food-stuffs as far as their entrance into the blood, we will now proceed to consider the blood itself.

The first thing that strikes us when we begin to examine the blood, and that which offers the greatest difficulties to chemical analysis, is the phenomenon of coagulation. As soon as the blood leaves the vessels of the living animal, a part of the proteids passes from the apparently soluble into the coagulated condition. The quantity of this colloid substance, commonly called fibrin, is relatively very small. It does not usually exceed from 0.1 to 0.4 per cent. of the weight of the blood. Nevertheless the passage of this small amount into the coagulated state converts the whole blood into a more or less solid jelly-like mass. On standing, this mass contracts, sometimes to half of its original volume, and squeezes out the contained fluid, whilst the corpuscles are almost wholly retained. Thus the coagulated blood separates into clot and serum. Serum is therefore plasma minus fibrin; the clot consists of the closely packed blood-corpuscles, with a small residue of serum and the coagulated proteid, or fibrin.

If, however, the blood be beaten with a glass rod whilst coagulation is proceeding, the coagulating substance attaches itself to the rod in the form of small fibrous masses, which coalesce with one another, and contract round the rod so that they can be removed with it. In this way so-called defibrinated blood is obtained, which remains fluid, and consists of serum with blood-corpuscles suspended in it. When we remember how great a tendency to pass into a coagulated modification is shown by all colloid bodies, the phenomenon of coagulation ought not to surprise us. Moreover, it is by no means a peculiarity of the blood. Lymph and chyle are likewise coagulable. The appearance of *rigor mortis* in dying muscle depends upon an essentially similar process, and it is probable that the death of every living vegetable and animal tissue is accompanied by a passage of a part of the proteid constituents from the fluid to the coagulated state. Coagulation of the blood is therefore not a vital process—it indicates the commencing dissolution of the dying blood; hence it might be thought that the subject of coagulation was beyond the scope of physiology.

The coagulation of the blood however subserves a very important process; it greatly aids in preventing bleeding when a blood-vessel is injured, and so far it may be considered as a physiological process, one of the means of self-preservation possessed by the organism.

The nature and causes of coagulation possess an extreme interest from a pathological point of view. For it is well known that, under certain pathological conditions, coagulation of the blood takes place in the vessels during life; and this process leads to disturbances of the most varied character, and may be a cause of death.

Hence it is a question of great importance to know what causes the blood to remain fluid under normal conditions in the vessels during life; what the exact nature of the whole process is; what the substance is which separates out; and what the causes of its separation are. In spite of many researches, we are not yet in a position satisfactorily to answer this question. The little that is positively known we will consider in detail. First of all, we know that the contact of the blood with the normal living vessel-wall prevents coagulation.[1] If, in a living animal, a blood-vessel be tied at two points, the enclosed stagnating blood does not coagulate for several hours, but it does so very quickly if it be allowed to escape from the vessel.

Brücke showed that the blood in the heart of the tortoise remained fluid after the heart had been removed from the body, when the vessels had been tied. If minute glass tubes were inserted into some of the vessels, so as to fit them exactly, and to prevent the blood from coming into contact with the wall of the vessel, it was found that the blood clotted in these tubes, but remained fluid elsewhere, in the other vessels and in the heart. Indeed, Brücke observed that any foreign body introduced into the blood became covered with a layer of fibrin.

When a vessel is ligatured, the blood after a time coagulates from the point ligatured down to the first branch given off from the vessel. The coagulation always starts from the ligatured spot, where the endothelium of the vessel is injured. It may also be supposed that the whole endothelial lining, from the

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[1] E. Brücke, Virchow's *Arch.*, vol. xii. pp. 81, 172 : 1857.

injured spot to the first branch, is altered and no longer normal, since it does not obtain the usual amount of specific nutriment in consequence of the stagnation of the blood.

In this way the occurrence of thrombosis, in consequence of atheromatous degeneration of the lining membrane, or as the result of the compression of the vessel by a new growth, &c., may be explained.[1]

We know further that the coagulation of the blood is constantly preceded by the death and breaking up of the white blood-corpuscles. It would appear that in some way or other the products of the breaking down of leucocytes enter into the formation of the clot.[2] Mantegazza pointed out that only those fluids are spontaneously coagulable which contain leucocytes, such as blood, lymph, and pathological transudations,[3] and that the fluids lose their power of clotting as soon as the leucocytes can be removed. Johannes Müller[4] had shown that, if frog's blood be diluted with a solution of sugar and filtered, the large red blood-corpuscles remain in the filter, whereas the filtrate coagulates. Johannes Müller therefore concluded that the coagulating matters arise from the plasma. But Mantegazza showed that the small and soft colorless blood-corpuscles get through the filter paper in this experiment, and that if the colorless corpuscles are retained by the use of very fine filter paper, the filtrate is not coagulable.[5]

When Mantegazza drew a silk thread through the vein of a living animal, he found that in two minutes it was covered with leucocytes, and some fibrin, which was commencing to form round them. If the experiment lasted longer, the thread

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[1] On the origin of thrombi *vide* Virchow's researches in his "Gesammelten Abhandlungen zur wissenschaftlichen Medicin," pp. 59–732 : Frankfurt a. M., 1856; further F. W. Zahn, Virchow's *Arch.*, vol. lxii. p. 81 : 1875; and J. C. Eberth and C. Schimmelbusch, Virchow's *Arch.*, vol. ciii. p. 39 : 1886 ; and vol. cv. pp. 331, 456 : 1886. A general survey of the literature of the subject is given here.

[2] The view that fibrin arose from the breaking up of the leucocytes was first adopted by William Addison, *London Medical Gazette*, new ser., vol. i., for the session 1840–1841, pp. 477, 689; and by Lionel Beale, *Quar. Journ. of Micros. Science*, vol. xiv. p. 47: 1864; subsequently by Paolo Mantegazza, "Ricerche sperimentali sull' origine della fibrina e sulla causa della coagulatione del sangue": Milano, 1871. A complete account of this work, by Boll, appeared in 1871, in the *Centralbl. f. d. med. Wissensch.*, p. 709 ; and in 1876 Mantegazza published his work in German in Moleschott's *Untersuch. z. Naturlehre des Menschen u. der Thiere*, vol. xi. pp. 523–577. Compare E. Tiegel, "Notizen über Schlangenblut," Pflüger's *Arch.*, vol. xxiii. p. 278 : 1880.

[3] Mantegazza, Moleschott's *Untersuch. z. Naturlehre*, vol. xi. pp. 552, 557.

[4] Johannes Müller, *Handb. d. Physiol. des Menschen*, 4th edit., vol. i. p. 104 : Coblentz, 1844.

[5] Mantegazza, *loc. cit.*, p. 556.

became surrounded with a strong white coagulum, which was always crowded with leucocytes. Other foreign bodies introduced into the blood-current behaved in the same manner, and moreover the rougher their surface the more extensive was the coagulum, and the more readily did the leucocytes attach themselves to it. No coagulum formed round a smooth thin platinum wire.[1]

Zahn[2] made similar experiments with the same result. If he introduced small glass rods with smooth surfaces into the heart of a living animal, no clot was produced. But if he roughened the rod with a file before insertion, a coagulum formed on the uneven surface. Zahn showed further that a grouping together and breaking up of leucocytes always precedes formation of a thrombus.

Finally, Alexander Schmidt has carried out very extensive experiments on the relation of colorless blood-corpuscles to coagulation.[3] He found that horse's blood was very suitable for this purpose, being possessed of two peculiarities in which it differs from the blood of other animals hitherto examined: firstly, it clots more slowly; and, secondly, the red blood-corpuscles sink far more rapidly. It is thus possible to remove the plasma which remains after the red corpuscles have sunk to the bottom, before coagulation sets in. By the use of cold, clotting is still further delayed. If the blood be allowed to run from a horse's vein straight into a vessel surrounded with ice, the red corpuscles fall completely to the bottom, and the specifically lighter colorless cells, which sink more slowly, form a layer over the red corpuscles (buffy-coat). The larger portion of the plasma can now be removed and filtered. The colorless cells remain in the filter, owing to the solid consistency acquired in the cold, which prevents their accommodation to the form of the filter-pores and their consequent

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[1] Mantegazza, Moleschott's *Untersuch. z. Naturlehre*, vol. xi. pp. 558–563.

[2] F. W. Zahn, *loc. cit.*, pp. 104–112.

[3] Alexander Schmidt has published an account of the main facts of his comprehensive researches, with the title, "Die Lehre von den fermentativen Gerinnungserscheinungen in den eiweissartigen thierischen Körperflüssigkeiten" (Dorpat, C. Mattiesen, 1876). Alexander Schmidt's more recent investigations on the coagulation of the blood are contained in the dissertations by his pupils for their doctorate:—" L. Birk and J. Sachsendahl, 1880; N. Bojanus and Ferd. Hoffmann, 1881; Ed. von Samson-Himmelstjerna and N. Heyl, 1882; H. Feiertag, F. Slevogt, Fr. Rauschenbach, and Ed. von Götschel, 1883; O. Groth and W. Grohmann, 1884; and Jacob von Samson-Himmelstjerna, 1885. Compare O. Hammarsten, Pflüger's *Arch.*, vol. xiv. p. 211: 1877; and vol. xxx. p. 437: 1883; L. Frédéricq, *Bullet. de. l'Acad. roy. de Belg.*, sér. ii. t. lxiv. No. 7: Juillet, 1877; *Ann. de la Soc. de Méd. de Gand.*: 1877; "Recherches sur la constitution du plasma sanguin," Gand, Paris, Leipzig, 1878; and L. C. Wooldridge, "The Nature of Coagulation," 1888.

passage; and a pure clear plasma is obtained as filtrate, which now clots very slowly and yields a very slight coagulum. If leucocytes from the filter be added to this plasma, abundant coagulation takes places. If all the blood, the coagulation of which had been prevented by cooling, be allowed to clot at the temperature of the room, the firmest coagulum occurs in the buffy-coat.

My Dorpat colleague has repeatedly been so kind as to show me these experiments with the uncoagulated horse's blood. The amount of leucocytes is most surprising. They are undoubtedly far more numerous than in defibrinated blood. But the extraordinary variety of the forms is still more astonishing: from the smallest colorless corpuscles, with a diameter hardly greater than that of the red corpuscles, such as one is accustomed to see in defibrinated blood, to the large granulated yellowish cells with nuclei, and a diameter of more than double—(Schmidt's granule masses).[1] After complete coagulation, these granule masses disappear. Schmidt and his pupils say that they have watched their breaking up into minute granules,[2] and the gradual change of the latter into the fibrin-coagulum, under the microscope. These granule masses, and the transitional forms between them and the ordinary colorless blood-corpuscles, appear to be much less numerous and to break up more rapidly in the blood of other mammals, so that it is difficult to obtain a view of them under the microscope.[3]

We are unable as yet to decide whether the *débris* of leucocytes are themselves a part of the material which forms the coagulum, or whether certain products of decomposition, resembling ferments, give the impulse for the passage of certain proteids of the plasma into the coagulated modification.

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[1] A diagram of these granule masses and their products of decomposition is given in the Dissertation of George Semmer, "Ueber de Faserstoffbildung im Amphibien- und Vogelblute und die Entstehung der rothen Blutkörperchen der Säugethiere": Dorpat, Mattiesen, 1874.

[2] Mantegazza also noticed the granules in the plasma from horse's blood (*loc. cit.*, p. 563).

[3] With the aid of the improved microscopes, small granules and "Plättchen" have recently been discovered in the blood, which are considered to be form-elements, and are supposed to participate in the coagulation of the blood. Alexander Schmidt explains these structures as being the *dêbris* of his granule masses. In this connection *vide* G. Hayem, *Compt. rend.*, vol. lxxxvi. p. 58: 1878; J. Bizzozero, Virchow's *Arch.*, vol. xc. p. 261: 1882; M. Löwit, *Sitzungsber. der Wiener Akad.*, vol. lxxxix. p. 270; and vol. xc. p. 80: 1884; and L. C. Wooldridge, in the "Beiträge zur Physiologie, Carl Ludwig zu seinem siebzigsten Geburtstage gewidmet von seinen Schülern," p. 221: Leipzig, Vogel, 1887.

The following observation must be cited as being particularly important. It appears that a part of the substances which excite coagulation remains in the blood after the separation of the fibrin Alexander Schmidt showed that, if defibrinated blood or serum be added to lymph or to serous transudations, which coagulate very slowly of themselves, and give very little fibrin, the fluid would soon be entirely converted into a gelatinous mass. The fluids of the pleural and the pericardial cavities of human beings and of horses are usually quite free from lymph-cells, and therefore uncoagulable. But they coagulate on the addition of blood-serum. The fact that coagulation occurs in the vessels after the transfusion of defibrinated blood is capable of the same explanation. Armin Köhler[1] showed that if blood were taken from a rabbit, defibrinated, and then injected into the vessels of the same animal, death ensued owing to clotting in the vessels. For this reason, the therapeutic use of transfusion has fallen into disuse.[2] An important contribution to the explanation of blood-clotting has been afforded by Arthus and Pagès,[3] who have shown that coagulation is prevented if all the lime salts be precipitated from the plasma by the addition of a small quantity of sodium oxalate or fluorid.[4]

From these remarks on the coagulation of the blood it may be seen what difficulties have to be encountered in the chemical examination of the blood, and especially in any attempt to obtain a separate quantitative analysis of plasma and of blood-corpuscles.

The pure unaltered plasma, as procured from horse's blood, according to Alexander Schmidt's method, has never been analyzed. The serum has been analyzed, and the composition of the plasma has been deducted from that of the serum. It was considered that the composition of the plasma was ascertained when the fibrin was added to the serum. But we now know that the calculation is not so easy. We do not know which constituents of the plasma take part in the coagulation, nor which products of the decomposition of lymph-cells pass

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[1] Armin Köhler, "Ueber Thrombose und Transfusion, Eiter und septische Infection, u. deren Beziehungen zum Fibrinferment": Dorpat, 1877.

[2] E. von Bergmann has published, in the form of a lecture, a very interesting account and criticism of the literature on the transfusion of blood, "Die Schicksale der Transfusion im letzten Decennium": Berlin, Hirschwald, 1883. Compare A. Landerer, Virchow's *Arch.*, vol. cv. p. 351: 1886.

[3] M. Arthus, "Recherches zur la coagulation du sang," Thèse, Paris, 1890. Arthus and Pagès, *Arch. de Physiol. norm. et path.*, vol. xxii. p. 739: 1890.

[4] [For discussion of the more recent work and views on the subject of the coagulation of the blood, the reader is advised to consult the article on this subject in Shäfer's "Text-book on Physiology," vol. i.]

into the serum. We do not know what should be removed from or what added to the serum in order to determine the composition of the plasma.

We are met by insuperable difficulties in the endeavor to free the red blood-corpuscles from the serum, and to analyze them in a pure state. The means adopted by chemists to separate a precipitate from a solution cannot be used in this case. The large blood-corpuscles of amphibia may be collected on the filter, but not those of mammals. This is not due to their minuteness; for they are far larger under the microscope than, for instance, the crystals of a precipitate of sulphate of barium or oxalate of lime, which do not go through the filter. The red blood-corpuscles pass through the filter, because, owing to their soft and yielding consistency, they adapt themselves to the form of the filter-pores. The method of decanting remains as a last resource, but this alone does not suffice, and must be followed by washing; but what liquid will serve for this purpose? The usual medium, water, cannot be employed in this case, for as soon as the red blood-corpuscles come into contact with water, the red coloring matter, hemoglobin, is dissolved. Now, as this forms the chief constituent of the red corpuscles, nothing remains but so-called stromata, reduced, pale, round, very feebly refractive, specifically light *débris.*[1]

If, instead of water, a dilute salt solution of a certain concentration be employed, *i. e.*, from 1½ to 3 per cent. of sodium chlorid, no change in the corpuscles apparent under the microscope takes place. If the solution of salt is stronger, they shrink; if more dilute they swell, and lose some of their hemoglobin in it.

By thus decanting and washing with dilute salt solution, the blood-corpuscles of defibrinated blood can be completely separated from all the constituents of serum. But do they retain their original constitution? May not the salt or the water pass into the blood-corpuscles; and, on the other hand, may not constituents of the blood-corpuscles have passed into the salt solution by osmosis? We can only be certain of one thing, and that is, that no hemoglobin has escaped, as this would be at once discovered by its brilliant color. It is likewise extremely probable that the genuine colloid substances, the proteids, which diffuse with great difficulty, do not quit the blood-corpuscles. We are therefore in a position to form a quantitative estimate of the quantity of hemoglobin

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[1] For the properties and constitution of the stromata, *vide* L. C. Wooldridge, Du Bois' *Arch.*, p. 387 : 1881.

and of proteid in the corpuscles of a definite amount of blood. If moreover the quantity of hemoglobin and of proteid in the total blood, and the amount of proteid in the serum, be estimated, we are in possession of all the figures necessary to compute the proportion that the weight of the serum bears to that of the blood-corpuscles in the total blood.

This is the method of quantitative analysis of the blood proposed by Hoppe-Seyler.[1] An example will serve to explain the method of computation.[2]

In 100 grms. of defibrinated pig's blood were found—

$$\left.\begin{array}{l}(a)\ 18.92\\(b)\ 18.88\end{array}\right\}\text{mean: } 18.90 \text{ proteids} + \text{hemoglobin.}$$

In the blood-corpuscles of 100 grms. of the same blood were found—

$$\left.\begin{array}{l}(a)\ 15.04\\(b)\ 15.13\\(c)\ 15.05\end{array}\right\}\text{mean: } 15.07 \text{ proteids} + \text{hemoglobin.}$$

In the serum of 100 grms. of blood—

$$18.90 - 15.07 = 3.83 \text{ grms. proteids.}$$

In 100 grms. of serum—

$$\left.\begin{array}{l}(a)\ 6.74\\(b)\ 6.79\end{array}\right\}\text{average: } 6.77 \text{ proteids.}$$

From this the amount of serum in 100 grms. of defibrinated blood may be computed—

$$\frac{3.83}{6.77}\cdot 100 = 56.6 \text{ per cent. serum.}$$
$$100 - 56.6 = 43.4 \text{ per cent. blood-corpuscles.}$$

An analysis of the total blood and another of the serum is now all that is necessary to enable us to compute the exact proportion of each constituent in defibrinated blood.

In order to prove the reliability of this method, I determined the proportion of the serum to the corpuscles in the same blood by another method. We are in fact able to estimate this proportion, as soon as we are in a position to ascertain accurately that any one of the constituents of the serum does not occur in the corpuscles. This is the case

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[1] Hoppe-Seyler, "Handb. der physiol. u. pathol. chemisch. Analyse," § 272, 5th edit., p. 441 : Berlin, Hirschwald, 1883. This method is rendered much more simple by the use of the centrifuge (*vide* L. von Babo, Liebig's *Annal.*, vol. lxxxii. p. 301 : 1852); without this, the repeated sinking of the blood-corpuscles for the purpose of decanting the fluid would necessitate a process occupying several weeks, and even at a low temperature decomposition and escape of hemoglobin would be unavoidable.

[2] G. Bunge, "Zur quantitativen Analyse des Blutes," *Zeitschr. f. Biolog.*, vol. xii. p. 191 : 1876.

with sodium in some kinds of blood. It was rendered probable by the earlier experiments of C. Schmidt[1] and of Hoppe-Seyler's pupil, Sacharjin,[2] and the following analyses made by myself put the matter beyond all doubt.

If defibrinated pig's blood be acted on by the centrifugal machine, the red corpuscles separate from the serum as a thick paste, which is found to be very poor in sodium. It contains seven times less sodium than the serum. Supposing the deposit to contain only one-seventh of its total bulk of serum, this would suffice to cover its whole amount of sodium. Now, there was no difficulty in determining by the microscope a considerable amount of interstitial fluid among the corpuscles. If the blood-corpuscles contain any sodium at all, it must be present in exceedingly minute quantities, and we should commit no serious error in determining the quantity of serum in blood, by calculating it from the amount of sodium in the blood and the serum.

The analysis and calculation gave the following results:—
In the total blood—

$$\left.\begin{array}{l}(a)\ 0.2403\\(b)\ 0.2409\end{array}\right\}\text{mean: } 0.2406 \text{ per cent. } Na_2O.$$

In serum—

$$\left.\begin{array}{l}(a)\ 0.4283\\(b)\ 0.4260\end{array}\right\}\text{mean: } 0.4272 \text{ per cent. } Na_2O.$$

$$\frac{0.2406}{0.4272}\times 100 = 56.3 \text{ per cent. serum.}$$

$$100 - 56.3 = 43.7 \text{ per cent. blood-corpuscles.}$$

The numbers agree remarkably with those obtained for the same pig's blood by Hoppe-Seyler's method.

In the case of the blood of the horse, I made an analysis according to Hoppe-Seyler's method, and found 46.5 per cent. serum, and 53.5 per cent. corpuscles; by means of the sodium calculation, the result was 46.9 per cent. of serum, and 53.1 per cent. of blood-corpuscles. This correspondence cannot be accidental. We must conclude from it (1) that Hoppe-Seyler's method gives correct results; and (2) that in the blood of the pig and the horse, the sodium occurs only in the plasma.

Unfortunately the latter conclusion is not true for all varieties of blood. In dog's and bullock's blood the corpuscles contain sodium as well as the serum. The easy and exact method for determining the relative proportions of corpuscles

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[1] C. Schmidt, "Charakteristik der epidemischen Cholera": Leipzig and Mitau, 1850.

[2] G. Sacharjin, "Zur Blutanalyse," Virchow's *Arch.*, vol. xxi. p. 387 : 1861.

and serum by means of the amount of sodium is in so far of very great value, as it enables us to put to the proof other methods which are applicable to all varieties of blood.

In the following tables the results of my analyses of blood are given :—

ONE THOUSAND GRAMMES OF DEFIBRINATED BLOOD CONTAIN—

	PIG.		HORSE.		BULLOCK.	
	436.8 CORPUSCLES.	563.2 SERUM.	531.5 CORPUSCLES.	468.5 SERUM.	318.7 CORPUSCLES.	681.3 SERUM.
Water	276.1	517.9	323.6	420.1	191.2	622.2
Solids	160.7	45.3	207.9	48.4	127.5	59.1
Proteid and hemoglobin . . .	151.6	38.1	—	—	123.6	49.9
Other organic substances	5.2	2.8	—	—	2.4	3.8
Inorganic substances	3.9	4.3	—	—	1.5	5.4
K_2O . . .	2.421	0.154	2.62	0.13	0.238	0.173
Na_2O	0	2.406	0	2.08	0.667	2.964
CaO	0	0.072	—	—	—	0.070
MgO	0.069	0.021	—	—	0.005	0.031
Fe_2O_3	—	0.006	—	—	—	0.007
Cl	0.657	2.034	1.02	1.76	0.521	2.532
P_2O_5	0.903	0.106	—	—	0.224	0.181

	One thousand grammes CORPUSCLES contain—			One thousand grammes SERUM contain—		
	PIG.	HORSE.	BULLOCK.	PIG.	HORSE.	BULLOCK.
Water	632.1	608.9	599.9	919.6	896.6	913.3
Solids	367.9	391.1	400.1	80.4	103.4	86.7
Proteid and hemoglobin .	347.1	—	387.8	67.7	—	73.2
Other organic substances . .	12.0	—	7.5	5.0	—	5.6
Inorganic substances	8.9	—	4.8	7.7	—	7.9
K_2O	5.543	4.92	0.747	0.273	0.27	0.254
Na_2O	0	0	2.093	4.272	4.43	4.351
CaO	0	—	0	0.136	—	0.126
MgO	0.158	—	0.017	0.038	—	0.045
Fe_2O_3	—	—	—	—	—	0.011
Cl . . .	1.504	1.93	1.635	3.611	3.75	3.717
P_2O_5	2.067	—	0.703	0.188	—	0.266

E. Abderhalden[1] has carried out two complete analyses of blood according to this method.

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[1] E. Abderhalden (Bunge's laboratory), *Zeitschr. f. physiol. Chem.*, vol. xxiii. p. 521: 1897.

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Analysis of Horse's Blood.

1000 parts Blood contain by Weight—		1000 parts Serum contain by Weight—		1000 parts defibrinated Blood contain—				1000 parts Corpuscles contain—	
				529.7	Corpuscles.	470.3	Serum.		
Water	749.02	Water	902.05	Water	324.79	Water	424.23	Water	613.15
Solids.	250.98	Solids	97.95	Solids	204.91	Solids	46.07	Solids	386.84
Hemoglobin.	166.9			Hemoglobin	166.9			Hemoglobin	315.08
Proteid	69.7	Proteid	84.24	Proteid	30.08	Proteid	39.62	Proteid	56.78
Sugar	0.526	Sugar	1.176	Sugar	—	Sugar	0.551	Sugar	—
Cholesterin	0.346	Cholesterin	0.298	Cholesterin	0.206	Cholesterin	0.140	Cholesterin	0.388
Lecithin	2.913	Lecithin	1.720	Lecithin	2.105	Lecithin	0.8089	Lecithin	3.973
Fat	0.611	Fat	1.390	Fat	—	Fat	0.6113	Fat	—
Phosphoric acid as nuclein.	0.060	Phosphoric acid as nuclein	0.020	Phosphoric acid as nuclein	0.0506	Phosphoric acid as nuclein	0.0094	Phosphoric acid as nuclein	0.095
Soda	2.091	Soda	4.434	Soda	—	Soda	2.0853	Soda	—
Potash	2.738	Potash	0.263	Potash	2.6143	Potash	0.1237	Potash	4.935
Iron oxid	0.828	Iron oxid	—	Iron oxid	0.828	Iron oxid	—	Iron oxid	1.563
Lime.	0.051	Lime	0.1113	Lime	—	Lime	0.0523	Lime	—
Magnesia	0.064	Magnesia	0.045	Magnesia	0.0429	Magnesia	0.0211	Magnesia	0.0809
Chlorin	2.785	Chlorin	3.726	Chlorin	1.0327	Chlorin	1.7523	Chlorin	1.949
Phosphoric acid.	1.120	Phosphoric acid	0.240	Phosphoric acid	1.0072	Phosphoric acid	0.1128	Phosphoric acid	1.901
Inorganic phosphoric acid	0.806	Inorganic phosphoric acid	0.0715	Inorganic phosphoric acid	0.7724	Inorganic phosphoric acid	0.0336	Inorganic phosphoric acid	1.458

Analysis of Bullock's Blood.

1000 parts Blood contain by Weight—		1000 parts Serum contain by Weight—		1000 parts defibrinated Blood contain—				1000 parts Corpuscles contain—	
				529.7	Corpuscles.	470.3	Serum.		
Water	808.9	Water	913.64	Water	192.65	Water	616.25	Water	591.858
Solids	191.1	Solids	86.36	Solids	132.85	Solids	58.249	Solids	408.141
Hemoglobin	103.10			Hemoglobin	103.10			Hemoglobin	316.74
Proteid	69.80	Proteid	72.5	Proteid	20.89	Proteid	48.901	Proteid	64.20
Sugar	0.7	Sugar	1.05	Sugar	—	Sugar	0.708	Sugar	—
Cholesterin	1.935	Cholesterin	1.238	Cholesterin	1.100	Cholesterin	0.835	Cholesterin	3.379
Lecithin	2.349	Lecithin	1.675	Lecithin	1.220	Lecithin	1.129	Lecithin	3.748
Fat	0.567	Fat	0.926	Fat	—	Fat	0.625	Fat	—
Phosphoric acid as nuclein	0.0267	Phosphoric acid as nuclein	0.0133	Phosphoric acid as nuclein	0.0178	Phosphoric acid as nuclein	0.0089	Phosphoric acid as nuclein	0.0546
Soda	3.635	Soda	4.312	Soda	0.7266	Soda	2.9084	Soda	2.2322
Potash	0.407	Potash	0.255	Potash	0.2351	Potash	0.1719	Potash	0.722
Iron oxid	0.544	Iron oxid	—	Iron oxid	0.544	Iron oxid	—	Iron oxid	1.671
Lime	0.069	Lime	0.1194	Lime	—	Lime	0.0805	Lime	—
Magnesia	0.0356	Magnesia	0.0446	Magnesia	0.0056	Magnesia	0.0300	Magnesia	0.0172
Chlorin	3.079	Chlorin	3.69	Chlorin	0.5901	Chlorin	2.4889	Chlorin	1.8129
Phosphoric acid	0.4038	Phosphoric acid	0.244	Phosphoric acid	0.2392	Phosphoric acid	0.1646	Phosphoric acid	0.7348
Inorganic phosphoric acid	0.1711	Inorganic phosphoric acid	0.0847	Inorganic phosphoric acid	0.1140	Inorganic phosphoric acid	0.0571	Inorganic phosphoric acid	0.3502

In order to give an idea of the composition of human blood, I subjoin the analysis of my revered teacher, Carl Schmidt,[1] one that has not yet been surpassed, though it may be remarked that the method employed gave too high an estimate for the corpuscles in proportion to the volume of blood.

BLOOD OF A MAN TWENTY-FIVE YEARS OF AGE.

One Thousand Grammes of Blood.

513.02 BLOOD-CORPUSCLES.

Water	349.69
Substances not vaporizing at 120°	163.33

Hematin	7.70	(including 0.512 iron)
'Blood-casein,' etc	151.89	
Inorganic constituents	3.74	(excluding iron)

Chlorin	0.898	=	Chlorid of potassium	1.887
Sulphuric acid	0.031		Sulphate of potassium	0.068
Phosphoric acid	0.695		Phosphate of potassium	1.202
Potassium	1.586		Phosphate of sodium	0.325
Sodium	0.241		Soda	0.175
Phosphate of lime	0.048		Phosphate of lime	0.048
Phosphate of magnesium	0.031		Phosphate of magnesium	0.031
Oxygen	0.206			
			Total	3.736

486.98 INTERSTITIAL FLUID (PLASMA).

Water	439.02
Substances not vaporizing at 120°	47.96

Fibrin	3.93
'Albumin,' etc	39.89
Inorganic constituents	4.14

Chlorin	1.722	=	Sulphate of potassium	0.137
Sulphuric acid	0.063		Chlorid of potassium	0.175
Phosphoric acid	0.071		Chlorid of sodium	2.701
Potassium	0.153		Phosphate of sodium	0.132
Sodium	1.661		Soda	0.746
Phosphate of lime	0.145		Phosphate of lime	0.145
Phosphate of magnesium	0.106		Phosphate of magnesium	0.106
Oxygen	0.221			
			Total	4.142

Specific Gravity = 1.0599.

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[1] C. Schmidt, "Charakteristik der epidemischen Cholera," pp. 29, 32: Leipzig and Mitau, 1850.

BLOOD OF A MAN TWENTY-FIVE YEARS OF AGE—(*continued*).

1000 GRAMMES OF BLOOD-CORPUSCLES.

Water	681.63
Substances not vaporizing at 120°	318.37

Hematin	15.02	(including 0.998 iron)
'Blood-casein,' etc.	296.07	
Inorganic constituents	7.28	(excluding iron)

Chlorin	1.750		Sulphate of potassium	0.132
Sulphuric acid	0.061		Chlorid of potassium	3.679
Phosphoric acid	1.355		Phosphate of potassium	2.343
Potassium	3.091	=	Phosphate of sodium	0.633
Sodium	0.470		Soda	0.341
Phosphate of lime	0.094		Phosphate of lime	0.094
Phosphate of magnesium	0.060		Phosphate of magnesium	0.060
Oxygen	0.401			
			Total of inorganic constituents (exclusive of iron)	7.282

SPECIFIC GRAVITY = 1.0886.

1000 GRAMMES OF INTERSTITIAL FLUID (PLASMA).

Water	901.51
Substances not vaporizing at 120°	98.49

Fibrin	8.06
'Albumin,' etc.	81.92
Inorganic constituents	8.51

Chlorin	3.536		Sulphate of potassium	0.281
Sulphuric acid	0.129		Chlorid of potassium	0.359
Phosphoric acid	0.145		Chlorid of sodium	5.546
Potassium	0.314	=	Phosphate of sodium	0.271
Sodium	3.410		Soda	1.532
Phosphate of lime	0.298		Phosphate of lime	0.298
Phosphate of magnesium	0.218		Phosphate of magnesium	0.218
Oxygen	0.455			
			Total of inorganic constituents	8.505

SPECIFIC GRAVITY = 1.0312.

1000 GRAMMES OF SERUM.

Water	908.84
Substances not vaporizing at 120°	91.16

Albumin, etc	82.59
Inorganic constituents	8.57

Chlorin	3.565		Sulphate of potassium	0.283
Sulphuric acid	0.130		Chlorid of potassium	0.362
Phosphoric acid	0.146		Chlorid of sodium	5.591
Potassium	0.317	=	Phosphate of sodium	0.273
Sodium	3.438		Soda	1.545
Phosphate of lime	0.300		Phosphate of lime	0.300
Phosphate of magnesium	0.220		Phosphate of magnesium	0.220
Oxygen	0.458			
			Total of inorganic constituents	8.574

SPECIFIC GRAVITY = 1.0292.

BLOOD OF A WOMAN THIRTY YEARS OF AGE.

One Thousand Grammes of Blood.

396.24 BLOOD-CORPUSCLES.

Water	272.56
Substances not vaporizing at 120°	123.68

Hematin	6.99	(including 0.489 iron)
'Blood-casein,' etc.	113.14	
Inorganic constituents	3.55	(excluding iron)

Chlorin	0.643	=	Sulphate of potassium	0.062
Sulphuric acid	0.029		Chlorid of potassium	1.353
Phosphoric acid	0.362		Phosphate of potassium	0.835
Potassium	1.412		Potash	0.340
Sodium	0.648		Soda	0.874
Phosphate of lime Phosphate of magnesium	0.086		Phosphate of lime Phosphate of magnesium	0.086
Oxygen	0.370			
			Total of inorganic constituents (excluding iron)	3.550

603.76 INTERSTITIAL FLUID (PLASMA).

Water	551.99
Substances not vaporizing at 120°	51.77

Fibrin	1.91
Albumin, etc.	44.79
Inorganic constituents	5.07

Chlorin	2.202	=	Sulphate of potassium	0.131
Sulphuric acid	0.060		Chlorid of potassium	0.270
Phosphoric acid	0.144		Chlorid of sodium	3.417
Potassium	0.200		Phosphate of sodium	0.267
Sodium	1.916		Soda	0.648
Phosphate of lime Phosphate of magnesium	0.332		Phosphate of lime Phosphate of magnesium	0.332
Oxygen	0.211			
			Total of inorganic constituents	5.065

Specific Gravity = 1.0503.

1000 GRAMMES OF BLOOD-CELLS.

Water	687.88
Substances not vaporizing at 120°	312.12

Hematin	18.48	(including 1.229 iron)
'Blood-casein,' etc.	284.68	
Inorganic constituents	8.96	(excluding iron)

Chlorin	1.623	=	Sulphate of potassium	0.157
Sulphuric acid	0.072		Chlorid of potassium	3.414
Phosphoric acid	0.913		Phosphate of potassium	2.108
Potassium	3.565		Potash	0.857
Sodium	1.635		Soda	2.205
Phosphate of lime Phosphate of magnesium	0.218		Phosphate of lime Phosphate of magnesium	0.218
Oxygen	0.933			
			Total of inorganic constituents (excluding iron of hemoglobin)	8.959

Specific Gravity = 1.0883.

BLOOD OF A WOMAN THIRTY YEARS OF AGE—(*continued*).

1000 GRAMMES OF INTERSTITIAL FLUID.

Water	914.25
Substances not vaporizing at 120°	85.75
Fibrin	3.16
Albumin, etc.	74.20
Inorganic constituents	8.39

Chlorin	3.647		Sulphate of potassium	0.217
Sulphuric acid	0.100		Chlorid of potassium	0.447
Phosphoric acid	0.237		Chlorid of sodium	5.659
Potassium	0.332	=	Phosphate of sodium	0.443
Sodium	3.173		Soda	1.074
Phosphate of lime Phosphate of magnesium	0.550		Phosphate of lime Phosphate of magnesium	0.550
Oxygen	0.351			
			Total of inorganic constituents	8.390

SPECIFIC GRAVITY = 1.0269.

1000 GRAMMES OF SERUM.

Water	917.15
Substances not vaporizing at 120°	82.85
Albumin, etc.	74.43
Inorganic constituents	8.42

Chlorin	3.659		Sulphate of potassium	0.218
Sulphuric acid	0.100		Chlorid of potassium	0.448
Phosphoric acid	0.238		Chlorid of sodium	5.677
Potassium	0.333	=	Phosphate of sodium	0.444
Sodium	3.183		Soda	1.077
Phosphate of lime Phosphate of magnesium	0.552		Phosphate of lime Phosphate of magnesium	0.552
Oxygen	0.351			
			Total of inorganic constituents	8.416

SPECIFIC GRAVITY = 1.0261.

Hemoglobin[1] therefore is the only organic substance which is peculiar to the red corpuscles. It also forms the chief constituent of the dried corpuscles. We have already considered the composition of hemoglobin and the question of its origin, and we shall shortly have to discuss the importance of hemoglobin in respiration (Lecture XVII.). The products of de-

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[1] A description of all the physical and chemical properties of hemoglobin would be beyond the scope of the present text-book. I therefore refer the reader to the accounts of Hoppe-Seyler in his *Med. chem. Unters.*: Berlin, 1866–1871; and to those of Hüfner and his pupils in the *Zeitschr. f. physiol. Chem.*; and in the latest volumes of the *Journ. f. prakt. Chem.* Compare also Nencki and Sieber, *Arch. f. exper. Path. u. Pharm.*, vol. xviii. p. 401: 1884; and vol. xx. pp. 325, 332: 1886.

composition will also be considered at a later period (Lectures XXI. and XXII.).

The organic substances found in serum are proteid, fat, soaps, cholesterin, lecithin, sugar, urea, kreatin, and a yellow coloring matter soluble in alcohol and ether, called lutein. Among the proteids, which make up the chief part of the organic substances, two groups are to be distinguished, the albumins and the globulins. The former are soluble, the latter insoluble, in water, but globulins are dissolved by dilute solutions of sodium chlorid. If serum be subjected to dialysis, the salts of the alkalies diffuse and the globulins are precipitated, whilst the albumins remain dissolved. The relative proportion of the two varies much. The result of starvation is to reduce the quantity of albumin and to increase the quantity of globulin. It would thus appear that globulin is the form which proteid assumes in its transference from one organ to another. We know that in starvation the more important organs, the centers of life, are nourished at the expense of the other organs, chiefly of the skeletal muscles.[1] Thus Voit[2] found that the brain and spinal cord of a cat, after thirteen days' starvation, had lost only 3.2 per cent. of its weight, the heart only 2.6 per cent.; the skeletal muscles, on the other hand, 30.5 per cent. Miescher found, in his observations already quoted (p. 79), that the Rhine salmon, during its sojourn in fresh water, eats nothing, and that the organs of reproduction, ovary and testes, increase at the expense of the muscles. Miescher[3] at the same time called attention to the fact that during this period the globulins of the blood, which are so similar to those of muscle, increase in quantity, and the maximum of this increase was found to correspond to the period of maximum growth of the ovary.

E. Tiegel[4] found in the blood serum of snakes, whose alimentary canal was empty, only globulin, and no albumin; whereas in the blood of snakes whilst digesting, both varieties of proteid were constantly present. Burckhardt,[5] Miescher's

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[1] Chossat, *Mém. présentés à l'Acad. des Sciences de l'Institut de France:* vol. viii.: 1843; Bidder and Schmidt, "Die Verdauungssäfte u. der Stoffwechsel," p. 327: 1852.

[2] C. Voit, *Zeitschr. f. Biolog.*, vol. ii. p. 355: 1866.

[3] F. Miescher-Rüsch, "Statistische u. biologische Beiträge zur Kenntniss vom Leben des Rheinlachses." Separatabdruck aus d. schweiz. Litteratursammlung zur internationalen Fischereiausstellung in Berlin, 1880, p. 211.

[4] E. Tiegel, Pflüger's *Arch.*, vol. xxiii. p. 278: 1880.

[5] Burckhardt, *Arch. f. exper. Path.*, vol. xvi. p. 322: 1883. The apparently contradictory results of G. Salvioli are probably due to the fact that the period of starvation was very short in his experiments. Moreover Salvioli used another method for separating the two proteids (Du Bois' *Arch.*, p. 268: 1881).

pupil, has shown that the globulins in the blood of starving animals are increased at the expense of the albumins.

The conclusions of Danilewsky,[1] that the muscles of an animal which have the least work to do are richest in globulin, harmonize with these observations. It would appear that the muscles are not only organs of locomotion, but also storehouses for proteid.

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[1] A. Danilewsky, *Zeitschr. f. physiol. Chem.*, vol. vii. p. 124: 1882.

LECTURE XV

LYMPH.[1]

The substances which pass from the blood into the other tissues, there to be used up by the cells as food, do not reach these elements directly through the capillary wall; but proceed first into the lymph spaces, which are present in all the tissues. In the same manner, the final products of the metabolism of each cell do not pass straight into the blood, but must first be taken up by the lymph which bathes all the tissue-elements.

The only exception to this rule is furnished by Bowman's capsule in the kidney, which is closely applied to the walls of the blood-vessels of the glomerulus without the intervention of any appreciable lymph space. This arrangement seems to be connected with particularly rapid and complete transference of urinary constituents from the blood to the renal tubules. If we consider how large an amount of urea is excreted by these paths, or moreover that only a small proportion of the total arterial blood-stream passes through the kidneys and remains but a short time in these organs, we shall see how necessary some such arrangement is.

Such a rapid passage of material from the blood does not appear to be essential in the other organs. Most physiologists have therefore conceived the idea that a large quantity of plasma is always proceeding through the capillary walls into the lymph spaces, thence penetrating the tissues, where every cell extracts the substance which it needs for its sustenance.

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[1] [Throughout this chapter the author takes no notice of any work on the subject of lymph-formation since the publication of Heidenhain's paper in 1891. For an account of the present state of the question the reader is referred to Schäfer's "Text-book of Physiology," vol. i. p. 285, *et seq.* It may here be merely mentioned that recent experiments of Starling, Cohnstein and others have tended to show that mechanical factors play a much larger part in the production and absorption of lymph than was imagined by Heidenhain. Ludwig ascribed the formation of lymph to the coöperation of several factors: (1) Filtration, depending on the difference of pressure between the blood in the capillaries and the extravascular fluid, and on the permeability of the capillary wall; and (2) on the osmotic interchanges determined by chemical changes, *i. e.*, metabolic activity of the tissue-cells. Recent investigations have served to confirm rather than to refute Ludwig's ideas on the subject.]

This interpretation seemed to be justified by the circumstance that the qualitative composition of the lymph is identical with that of the plasma. Quantitatively however there is a difference; for, while the inorganic salts contained in the lymph are alike in amount and composition to those in the plasma, the amount of proteid in the lymph is much smaller than in the blood-plasma.

No definite conception has been formed concerning the mode in which the constituents of the plasma traverse the capillary wall. It is not possible that they can pass through by diffusion, since the colloid proteid would be left behind in the blood. The filtration hypothesis is equally untenable, since by this means all the constituents of the plasma would proceed to the lymph spaces in the same proportion as they occur in the blood. A compromise was therefore struck between diffusion and filtration, and it was sought to explain that the lymph is rich in diffusible constituents—salts, and relatively poor in non-diffusible substances—proteids. Only a very hazy notion could be formed concerning the nature of this process, therefore a suitable epithet was hailed in the word "transudation," the lymph being called the "transudate of the plasma."

These theories had to be abandoned when the processes came to be tested quantitatively by measuring the lymph-stream.

In twenty-four hours about 600 c.cm. of lymph flows through the thoracic duct of a dog 10 kg. in weight.[1]

If we assume that the flow of lymph is as slow in man as in the dog, it would amount to about 4 liters, in proportion to the body-weight. The small quantity of lymph flowing through the right thoracic duct into the blood may be disregarded.

This stream of lymph is much too slow to justify the assumption that all the cells derive their nourishment from it. This statement may be proved by a simple calculation.

Normal plasma contains only from 1 to 2 grm. sugar to the liter. In the course of the twenty-four hours therefore at most 8 grms. of sugar would be conveyed to the tissues in the 4 liters of transuded plasma. This amount is certainly not a sufficient one. As a matter of act in one day 500 to 1000 grms. of sugar are taken up from the intestines into the blood (Lecture XIII.). This amount is not destroyed in the blood itself (compare Lecture XVII.). It must therefore reach the tissues through the capillary walls. Hence it follows that a very concentrated solution of sugar traverses the cell-walls in those tissues where

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[1] Vide Heidenhain, Pflüger's *Arch.*, vol. xlix. p. 216: 1891. There the figures for the amounts of lymph in dogs are given. Compare also Lecture XIII.

a rapid consumption of sugar as a source of energy takes place, as for instance in the muscles, or where there is a storing up of material free from nitrogen, such as glycogen or fat, as in the liver or in the connective tissues.[1]

We may adduce another example.[2] The milk of animals which develop rapidly is very rich in lime. Dog's milk has from 4 to 5 grms. of lime to the liter.[3] A bitch from 20 to 30 kg. bodyweight secretes in twenty-four hours as much as $\frac{1}{2}$ liter of milk, which contains therefore from 2 to $2\frac{1}{2}$ grms. of lime. A liter of plasma contains only about 0.2 grm. of lime,[4] or from 10 to 12 times less than the milk. If therefore the epithelial cells of the mammary glands take the material they need for the formation of the milk from the transuded plasma, at least 10 liters of plasma would have to flow through the mammary glands in the twenty-four hours. This is not possible: only from 1 to 2 liters of lymph flow through the whole body—how much less therefore must flow through the mammary glands? Hence it follows that a fluid very rich in lime must be exuded from the blood capillaries in their course through the mammary glands, or, in other words, that the endothelial cells of the capillary wall must exercise a power of selection, as in fact does every cell, every living being.

That the capillary wall is able to give out substances in a much more concentrated state of solution than that in which they are contained in the plasma may be seen from the capillaries of the kidney. The plasma contains at most 1 grm. urea to the liter, the urine may contain as much as 40 grm. or even more.[5] Heidenhain[6] has shown that, after the injection of solutions of sugar into the blood, the amount of sugar in the lymph rises more than that in the blood plasma.

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[1] [This and the following example will serve as a criticism of the views of Bartholini but not of those of Ludwig. The passage of sugar or other diffusible substance from blood to tissue-cell occurs by diffusion. The consumption of any substance, whether it be oxygen or glucose, by a tissue-cell, leads to a diminished tension of this substance in the neighborhood of the cell; and a passage by diffusion of the substance naturally occurs from blood through lymph-space to cell. Such a process is absolutely independent of lymph-flow, and would occur if there were no fresh lymph production at all. An argument therefore as to the concentration of the transudation from the vessels which is based on the consumption of a substance by any given tissue, has no bearing on the point in question.]

[2] These two examples were introduced by myself as arguments against the prevailing views on the flow of plasma at the International Physiological Congress held at Basel in September, 1889, during the discussion which arose after Heidenhain's address.

[3] Bunge, *Zeitschr. f. Biolog.*, vol. x. pp. 301 and 303: 1874.

[4] In 1 liter of dog's serum I found 0.176 CaO. The figure must be somewhat raised for the plasma, since a little lime is carried down with the fibrin.

[5] *Vide* Lecture XXI. for the composition of urine in man when on a meat diet.

[6] *Loc. cit.*, p. 63, *et seq.*

In every organ and in every tissue the capillary wall allows a fluid of special constitution to pass through it, according to its various requirements: in the muscles this fluid is richer in sugar, in the mammary glands, in lime, and so on. After these special substances have been utilized, these fluids flow back into the main lymph-trunks, so that the mixture takes on a composition very similar to that of the original plasma. The lymph is therefore probably of very different constitution in the lymph-spaces of the various tissues. The analysis of lymph taken from the large lymphatics cannot give us any information as to the composition of the tissue-fluids themselves.

For those who wish to maintain the old theory of diffusion and to consider the capillary wall as a dead membrane passively concerned in the operation, the cells may be regarded as taking from the lymph the special substances which they need, converting them into an insoluble or colloid combination, which has thus lost all power of diffusion, *e. g.*, sugar into glycogen or fat, the soluble into insoluble compounds of lime. In this way the special substance would become less concentrated in the lymph than in the plasma, and a fresh supply would be continually passing according to the laws of diffusion through the capillary walls from the blood into the lymph, without the simultaneous passage of water. But there is really no reason for refusing to the capillary walls of the endothelial cells the 'active' functions which it is allowed are involved in the case of all other cells. However this may be, the old idea of the plasma stream[1] must be relinquished.

Impossible as it is for the food-stuffs to be conveyed to the various cells by a stream of plasma common to all alike, so it is equally impracticable for the end-products of metabolism to be returned by the common lymph stream to the blood. We must rather assume that these final products penetrate through the neighboring lymph-spaces into the nearest capillaries.

The most important of these waste materials, carbonic acid, can be proved to make its exit in this manner. The tension of CO_2 is less in the large lymph-trunks than in the blood (compare Lecture XVIII.). Moreover the lymph-flow is much too slow to carry off the large amounts of carbonic acid quickly enough. The passage of 800 to 1000 grms. of this gas through these organs in the twenty-four hours could not be effected unless the CO_2 were conveyed directly into the circulation. And this is probably the case with urea and the other end-products of metabolism. We must assume that these latter reach the

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[1] [*I. e.*, the irrigation theory of Bartholini.]

blood directly through the capillary walls and not through the medium of the lymph.

We have now to ask: What are the functions of the lymph? What are the objects of the lymph-spaces? Might not the interchange of material proceed in all the other organs as it does in the glomeruli of the kidney?

In the first place, the lymph-spaces have a purely mechanical use, inasmuch as they enable the blood-vessels to alter their lumen and so regulate their pressure. Were the blood-vessels surrounded with rigid tissue, this would be impossible. They need to be set in a compressible medium, which can adjust itself to the variations of the vascular lumina. Secondly, supposing that every cell were in immediate contact with a capillary vessel, as in the Malpighian glomerulus, the capillary system would become so enlarged that the circulation of the blood would become too much slowed down.

These considerations however refer to the uses of the lymph-spaces only, and not to those of the larger lymphatics. They do not explain why the fluid collects from the lymph-spaces into larger and larger vessels, which finally empty themselves into the blood-stream. Could not the food-stuffs pass through the capillary wall of the blood-vessels straight into the lymph-spaces, and, conversely, could not the final products of metabolism find their way directly from the lymph-spaces through the capillary wall into the blood? What is the need for a special stream of lymph?

In answering this question we have an indication in the fact that in the course of the lymphatics are interposed lymphatic glands, in which the lymph-cells are being continually formed by division.

We do not yet know very much of a definite character concerning the cells of the lymph, the leucocytes; although they undoubtedly are of great importance in the animal economy. We know that they can make their way out through the capillary wall and wander among the tissues. They may be seen assembling in masses wherever injurious substances are formed, where foreign bodies, poisonous matters, or micro-organisms penetrate the tissues, as well as in cases of inflammation and all kinds of pathological processes which accompany the degeneration of tissue. It appears that their function is to clear away the products of tissue-disintegration[1] and to render noxious substances harmless. They may be seen enclosing

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[1] An account of the literature on the behavior of leucocytes under normal and pathological conditions is given in the monograph of Herm. Rieder, "Beitr. z. Kenntniss der Leucocytose." Leipzig, Vogel: 1892.

within their protoplasm solid particles, or invading microorganisms;[1] and it is probable that they also take up and alter substances in a fluid and dissolved condition. I have already mentioned the part which has been ascribed to them in the absorption of proteid, in the regeneration of peptone into proteid within the intestinal wall, and in the conveyance of the peptone which reaches the blood in this form.

Now there is a constant disintegration of lymph-cells going on. We know, for instance, from Stöhr's experiments[2] that leucocytes emigrate in masses through the epithelium from the adenoid tissue of the tonsils and of the follicles of the tongue, as well as from the follicles of the whole intestinal and bronchial mucous membranes. Stöhr considers that an expulsion of "used-up material" is involved. These leucocytes must be replaced by the formation of new ones in the lymph-glands and by a supply of young cells passing with the lymph into the blood.

Finally the lymph-glands may have the function of altering the various kinds of lymph which flow into them from all the tissues, so as to assimilate it to the plasma before it enters the circulation. Without such previous assimilation a fluid, which had been changed by the processes of metabolism in the tissues, might either disintegrate the blood-corpuscles when it passes into the blood-stream or do mischief in some other direction.

It is known that injurious substances of all kinds, as well as microörganisms, are detained in the lymph-glands so that they cannot enter the blood, there to be passed on to the tissues. With this fact is also connected the swelling of the lymph-glands as a result of infection.

In the following table I append some of the most reliable analyses as examples of the composition of lymph.

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[1] It is well known that El. Metchnikoff was the first author to introduce the view that the leucocytes wage war against the intruding microörganisms and other injurious and foreign substances—the so-called doctrine of phagocytosis. *Arb. a. d. Zoolog. Inst. zu Wien*, vol. v. Hft. ii.: 1883; *Biolog. Centralbl.*, vol. iii.: 1883–1884; Virchow's *Arch.*, vol. xcvi. p. 177: 1884; vol. xcvii. p. 502: 1884; vol. cvii. p. 209: 1887; vol. cix. p. 176: 1887; vol. cxiii. p. 63: 1888: *Annales de l'Institut Pasteur*, p. 321: 1887; p. 604: 1888. [See also his work, "The Pathology of Inflammation," Paris, 1892, translated by E. H. Starling. London, Kegan Paul & Co., 1893.] This doctrine has been the subject of much dispute. Compare Baumgarten, *Berlin. klin. Wochenschr.*, p. 818: 1884; and *Centralbl. f. klin. Med.*, No. 26: 1888; and Weigert, *Fortschr. d. Med.*, p. 732: 1887; and p. 83: 1888. On the other hand a highly interesting observation, which bears out Metchnikoff's theory, has been recently published by Vaillard & Vincent: *Annales de l'Institut Pasteur*, Année 5, p. 34: 1891.

[2] Ph. Stöhr, *Biolog. Centralbl.*, vol. ii. p. 368: 1882; *Sitzungsber. d. physik. med. Ges. zu Würzburg*, May 19, 1883; Virchow's *Arch.*, vol. xcvii. p. 211: 1884.

To these I have added a few analyses of the 'pathological transudations,' ascitic fluid, pleural and pericardial effusions, dropsical fluid, and hydrocele fluid, which are considered by most authors as lymph increased above the normal by pathological conditions and obstructed absorption. Even the fluid contained in the ventricles of the brain, which it is well known may be increased largely in disease (*e. g.*, hydrocephalus), is regarded as lymph by many authors because the ventricles of the brain communicate by means of the *foramen of Magendie* with the lymph-spaces of the subarachnoid tissue. Some observers however deny that this communication exists. It must also be remembered that the ventricles of the brain are covered with epithelium, and that the fluid in them might be a specific secretion of these cells. The cerebro-spinal fluid is not spontaneously coagulable.

Finally, I have included a few analyses of chyle in Table I. I have already shown that the chyle of fasting animals is nothing but lymph, and that fat droplets are mixed with this lymph only during the digestion of fatty food (Lecture XIII.).

I. C. Schmidt, "Charakteristik der epidemischen Cholera." Mitau u. Leipzig, p. 29 : 1850. II. and III. Gubler & Quévenne, *Gaz. Méd. de Paris*, Nos. 24, 27, 30, and 34: 1854. The different specimens of lymph were obtained by pricking the varicose enlargements of the lymph-vessels in the skin of a woman's thigh. As the woman, with the exception of this lymph obstruction, was otherwise in a normal condition, we may perhaps regard this as ordinary lymph. IV. Rees, *Phil. Trans.*, p. 81: 1892. V. Hoppe-Seyler, "Physiol. Chem.," Berlin, Hirschwald, p. 597 : 1881. Effusion of chyle into the peritoneal cavity in consequence of rupture of the chyle-vessel. The chyle was obtained by tapping the abdomen. Hoppe-Seyler thought that it was undoubtedly normal chyle. VI. C. Schmidt, *loc. cit.*, p. 140. VII. and VIII. Hoppe-Seyler, *loc. cit.*, p. 505. IX.–XI. Herm. Nasse, "Ueb. Lymphe u. deren Bildung," *Akad. Gelegenheitschr.*, Marburg, 1872. XII. C. Schmidt, *loc. cit.*, p. 138. Taken from the same dog from which the blood for Analysis VI. was drawn. XIII.–XVII. C. Schmidt, *Bulletin de St. Petersbourg*, vol. iv. p. 355 : 1861.

I.–III. V. Hensen and C. Dähnhardt, Virchow's *Arch.*, vol. xxxvii. p. 55 : 1866. Both legs of the patient were swollen from the extensive thickening of the subcutaneous tissue and corium ; heart failure and ascites were also present. IV.–VI. Hoppe-Seyler, Virchow's *Arch.*, vol. ix. p. 250 : 1856. VII. Gorup-Besanez, "Lehrb. d. physiol. Chem.," 3d edit., p. 415. Braunschweig, Vieweg and Sohn, 1874. VIII. Wachsmuth, Virchow's *Arch.*, vol. vii. p. 334 : 1855. IX. Hoppe-Seyler, "Physiolog. Chem.," Berlin, Hirschwald, p. 605 : 1881. X. Scherer, *Verhandl. d. med. phys. Ges. zu Würzburg*, vol. vii. p. 268 : 1857. XI. Hammarsten, *Upsala Läkareförenings Förhandlingar*, vol. xiv. p. 33 : 1878. XII.–XV. C. Schmidt, "Charakteristik d. epidem. Cholera," Leipzig u. Mitau, pp. 122 and 123 : 1850. XVI.–XVIII. Hoppe-Seyler, Virchow's *Arch.*, vol. ix. p. 250 : 1856.

I.–V. Hoppe-Seyler, Virchow's *Arch.*, vol. xvi. p. 391 : 1859. VI. and VII. Halliburton, *Journ. of Physiol.*, vol. x. pp. 233 and 234 : 1890. VIII. and IX. C. Schmidt, "Charakteristik de epidem. Cholera," Leipzig and Mitau, pp. 135–138 : 1850. X. C. Schmidt, *loc. cit.*, p. 136. "Fluid between the dura mater and the vault of the skull, which was greatly expanded." XI. Hoppe-Seyler, *loc. cit.*

TABLE I.—*Normal Transudations, Compared with Normal Blood-plasma.*

	MAN.					DOG.							HORSE.				
	I.	II.	III.	IV.	V.	VI.	VII.	VIII.	IX.	X.	XI.	XII.	XIII.	XIV.	XV.	XVI.	XVII.
		Lymph.							Lymph from Cervical Lymphatic. H. NASSE.				Analyses by C. SCHIMDT.				
	Human Blood-plasma. C. SCHMIDT.	GUBLER and QUÉVENNE.		Chyle from a Beheaded Criminal.—REES.	Chyle. HOPPE-SEYLER.	Blood-plasma (Dog). C. SCHMIDT.	Blood-serum. HOPPE-SEYLER.	Chyle from the same Dog. HOPPE-SEYLER.	Fasting.	On Meat Diet.	On Vegetable Diet.	Liquor Cerebro-spinalis. C. SCHMIDT.	Blood-serum from a Foal.	Lymph from Cervical Lymphatic of a Foal.	Lymph from Cervical Lymphatic of a Foal.	Chyle of a Foal.	Chyle of a Foal.
Water	901.5	939.9	934.8	904.8	940.7	910.6	936.0	906.8	954.7	953.7	958.2	988.2	930.8	963.9	955.4	961.0	956.2
Dried subs.	98.5	60.1	62.5	95.2	59.3	89.4	64.0	96.2	45.3	46.3	41.7	11.8	69.2	36.1	44.6	39.0	43.8
Fibrin	8.1	0.5	0.6	70.8	—	6.0	—	1.1	0.6	0.7	0.5	2.4	—	28.8	2.2	30.5	1.3
Proteid	81.9	42.7	42.8		36.7	74.6	45.2	21.1	—	—	—		56.7		35.0		34.2
Extractives	—	5.7	4.4	—	—	—	—	—	—	—	—		3.9				
Fat	„	—	—	—	7.2	—	6.8	—	—	—	—		—			0.1	0.5
Lecithin		3.8	9.2	—	0.8	—		64.9	—	—	—		—			—	—
Cholesterin		—	—	—	1.3	—		—	—	—	—		—			—	—
Soaps	—	—	—	—	2.4	—	—	—	—	—	—		1.6			0.8	0.3
Ash	8.5	7.3	8.2	—	7.2	8.8	8.8	7.9	—	—	—	9.4	7.1			7.6	7.5
K	0.31	—	—	—	—	0.29	—	—	—	—	—	1.84	—	—	—	—	—
Na	3.41	—	—	—	—	3.49	—	—	—	—	—	2.52	—	—	—	—	—
Cl	3.54	—	—	—	—	3.30	—	—	—	—	—	4.91	—	—	—	—	—
NaCl	5.84	—	—	—	—	5.43	—	—	6.72	6.50	6.77	—	5.74	5.43	5.67	5.76	5.84
Na_2O	1.50	—	—	—	—	1.82	—	—	—	—	—	—	0.87	1.50	1.27	1.31	1.17
K_2O	0.37	—	—	—	—	0.35	—	—	—	—	—	—	0.14	0.03	0.16		0.13
Phosphates of alkal. earths	0.52	—	—	—	—	0.84	—	—	—	—	—	—	0.21	0.22	0.26	0.44	0.20
P_2O_5 not with alkal. earths	0.15	—	—	—	—	0.17	—	—	—	—	—	—	0.01	0.02	0.02	0.01	0.04

Table II.—*Pathological Transudations (Man).*

	I.	II.	III.	IV.	V.	VI.	VII.	VIII.	IX.	X.	XI.	XII.	XIII.	XIV.	XV.	XVI.	XVII.	XVIII.
	Human Lymph from a Fistula in the Thigh.			Peritoneal Transudation in a case of Cirrhosis of the Liver. Hoppe-Seyler.			Liquor Pericardii.			Hydrocele.		Pleural Transudation.	Peritoneal Transudation.	Edema of the Skin.	Fluid from Ventricles of Brain.	Pleural Transudation.	Peritoneal Fluid.	Edema of the Feet.
	Hensen and Dähnhardt.			First Tapping.	Second Tapping.	After Death.	Analysis by Gorup-Besanez.	Wachsmuth.	Hoppe-Seyler.	Analysis by Scherer.	Hammarsten. Mean of 17 Analyses.	From one and the same subject. C. Schmidt.				From one and the same subject. Hoppe-Seyler.		
Water . . .	987.7	986.1	985.2	984.5	982.5	983.3	955.1	962.5	961.8	957.6	938.9	964.0	978.9	988.7	983.5	957.6	967.7	982.2
Dried subst.	12.3	13.9	14.8	15.5	17.5	16.7	41.9	37.5	38.2	42.4	61.1	36.0	21.1	11.3	16.5	42.4	32.3	17.8
Fibrin . . .	2.6	—	—	—	—	—	0.8	—	—	0.4	0.6	28.5	11.3	3.6	8.0	—	—	—
Proteid		—	—	6.2	7.7	61.1	24.7	22.8	24.6	34.7	49.4					27.8	16.1	3.6
Extractives .	1.3	—	—	—	—	—	12.7	—	—	—	—					—	—	—
Fat, lecithin, cholesterin	0.03	—	—	—	—	—	—	—	—	9.2	4.0					—	—	
Ash	8.4	—	—	8.5	8.1	8.2	6.7	—	—	7.2	9.3	7.6	9.8	7.7	8.5	—	—	9.0
NaCl . . .	6.15	—	—	—	—	—	—	—	—	—	6.19	—	—	—	—	—	—	—
Na_2O . . .	0.57	—	—	—	—	—	—	—	—	—	1.09	—	—	—	—	—	—	—
K_2O	0.50	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
CaO	0.13	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—

TABLE III.—*Cerebrospinal Fluid from Cases where this was Abnormally Increased (Man).*

	I.	II.	III.	IV.	V.	VI.	VII.	VIII.	IX.	X.	XI.
	Spina bifida.					Woman 19 Years Old.	Child 11 Days Old.	Acute Meningeal Effusion. Case I.	Case II.	Fetus dying at or shortly before Birth.	Hydrocephalus in an Infant 5 Months Old.
	Three Tappings of the same Case.			Two Tappings of the same Case.				Fluid from Lateral Ventricles.			
	HOPPE-SEYLER.			HOPPE-SEYLER.		HALLIBURTON.		C. SCHMIDT.		C. SCHMIDT.	HOPPE-SEYLER.
Water	987.5	986.9	986.7	989.3	989.8	989.8	989.9	986.8	984.6	980.8	989.5
Dried subst.	12.5	13.1	13.3	10.7	10.2	10.2	10.1	13.2	15.4	19.2	10.5
Proteid	1.6	2.6	2.5	0.25	0.55	0.84	1.6	3.7	6.5	10.4	0.70
Extractives	—	—	—	—	—	—	—			0.95	—
Fat, lecithin, cholesterin	—	—	—	—	—	—	—				—
Ash	—	—	—	—	—	—	7.8	9.5	8.9	7.9	8.2
K	—	—	—	—	—	—	—	1.19	0.87	0.22	—
Na	—	—	—	—	—	—	—	3.32	3.48	3.15	—
Cl	—	—	—	—	—	—	—	3.73	3.20	3.78	—
Phosphates of alkaline earths	—	—	—	—	—	—	—	0.31	0.36	0.27	—
P_2O_5 not combined with alkaline earths . . .	—	—	—	—	—	—	—	0.33	0.26	0.06	—

From these tables it may be seen that the lymph drawn from different parts of the body is highly variable in its composition, and especially as regards its proportion of proteid. This is also the case with the pathological transudations. The amount of proteid varies between 0.3 and 4.9 per cent. The quantity of fibrin is always less than in the blood; it varies in the lymph between 0.04 and .02 per cent., in the blood between 0.2 and 0.4 per cent.

The proportion of the two kinds of proteid, the globulins and the albumins, varies in the lymph between as wide limits as they do in the blood-plasma (compare Lecture XIV.). Experiments made so far on this subject have given the noteworthy results[1] that if blood, lymph, and chyle, or blood and a pathological transudation be taken from one and the same individual, these two kinds of proteid are nearly always present in the same proportion in the transudations and in the lymph, however great the difference may be in the total amount of proteid.

We cannot, within the scope of this book, treat of the causes and mode of formation of the pathological transudations. We know that nerve fibers run to every single endothelial cell of the capillary wall, and that therefore disturbances in the innervation of the capillary wall may be reflexly transmitted from any organ to any other organ. We must likewise remember that every mechanical disturbance of the circulation and every change in the chemical composition of the blood interfere with the normal nutrition of the capillary wall and lower the power of resistance possessed by the endothelial cells, so that they are not so capable of preventing the escape of constituents of the blood-plasma. Finally, we must not forget that abnormal constituents of all kinds act directly as irritants on the endothelial cells of the capillary wall, so soon as they enter the blood, and may thus alter their functions. The cause of the formation of transudations, which have been pathologically increased and altered, may therefore be of a very varying character in different organs. Their study must for the present be left to the domain of special pathology, where the results so far attained in physiological experiment may be utilized. A critical account of the physiology of lymph may be found in the work of Heidenhain already referred to.

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[1] G. Salvioli, Du Bois' *Arch.*, p. 268: 1881; F. A. Hoffmann, *Arch. f. exp. Path. u. Pharm.*, vol. xvi. p. 133: 1882.

LECTURE XVI

THE SPLEEN

Before leaving the subject of lymph and the lymphatic glands, we will take for our consideration another organ which is supposed to have similar functions, *viz.*, the spleen.

With the single exception of the amphioxus, the spleen is invariably present in all vertebrates, and is in all cases of very similar structure.

There is however an essential difference between the spleen and the lymphatic glands, in that the leucocytes formed in the spleen enter directly into the blood-stream. The blood of the splenic vein contains more leucocytes than the arterial blood. This was shown by Kölliker and Hirt,[1] whose experiments were afterwards confirmed by numerous observers.[2] In his investigations on the metabolism of Rhine salmon (*vide* p. 79), Miescher[3] carried out a number of very careful estimates on this point, the average number of white corpuscles to every 100 red blood-corpuscles being

Cardiac Blood.		Splenic Blood.		
♂	♀	♂	♀	
1.79	1.79	8.31	7.1	white corpuscles.

The earliest investigations on the functions of this organ dealt with the effects of its extirpation. Even Pliny[4] mentions as well known the fact that dogs will survive the extirpation of the spleen. Since that time occasional extirpations of the spleen have been successfully performed on different animals.[5] But it is only since the aseptic treatment of wounds has

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[1] Hirt, "De copia relat. corpusc. sanguin. alb.," Dissert. Leipzig: 1855.

[2] P. Emelianow, *Arch. d. Sciences biolog.*, St. Pétersbourg, vol. ii. p. 145: 1893. The earlier literature is here quoted.

[3] Miescher, Du Bois' *Arch.*, Anat. Abth., p. 212: 1881.

[4] Plinius, "Histor. naturalis.," lib. xi. c. xxxvii.

[5] An account of the earliest literature on extirpations of the spleen is given by G. Adelmann, *Deutsche Klinik*, p. 183: 1856.

been introduced that these operations have formed the bases of systematic series of experiments. Among the latest researches of this nature we may mention the following: Guido Tizzoni[1] cut out the spleen in eighteen rabbits, young and old. The longest time during which the animal was under observation was 240 days. He could discover no ill effects from the operation. In the young animals the growth proceeded as usual, and in adults the sexual functions were undisturbed and healthy offspring were produced. In the same way, Kourlow[2] found that guinea-pigs bear extirpation of the spleen well, and that they grow and propagate like normal animals. A. Dastre[3] cut out the spleen in young dogs, cats, rats, and guinea-pigs, and compared their rate of growth with that of normal animals from the same litter. He could discover no difference. Unfortunately the observation lasted but a short time—only four months in the case of the cats, and until they were full-grown in the case of the guinea-pigs.

The question now arises as to whether, if the animals survive the removal of their spleen, changes may not occur in one or other of their functions. Alterations in blood formation were especially anticipated. Of the numerous experiments made in this connection may be mentioned the most recent. P. Emelianow[4] found that, after extirpation of the spleen in dogs, the number of red blood-corpuscles diminished, while that of the white was increased. O. Vulpius,[5] experimenting on rabbits and goats, also observed that, when the spleen was excised, the red blood-corpuscles decreased by not more than 20 per cent., but that this diminution was made up after about a month had elapsed. The number of white blood-corpuscles immediately after the operation rose to double the normal, the increase however lasting at the most nine weeks.

From this increase of white and diminution of red blood-corpuscles it is natural to conclude that in the spleen the

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[1] G. Tizzoni, *Archivio per le scienze mediche*, vol. viii. No. 13, p. 255. Summarized in *Arch. ital. d. Biol.*, vol. vi. p. 103: 1884.

[2] Kourlow, Vratsch, Nos. 23, 24, 1889; No. 19, 1892 (Russian).

[3] A. Dastre, *Comptes rend. Soc. Biol.*, p. 584: 1893; and *Arch. d. Physiol.*, July, 1893.

[4] P. Emelianow, *Arch. d. Sciences biol.*, St. Pétersbourg, vol. ii. p. 157: 1893. The earlier literature is here quoted.

[5] O. Vulpius, *Beitr. z. klin. Chir.*, vol. xi. p. 684: 1894. This author gives a summary of the earlier and very abundant literature on the influence of excision of the spleen on the amount of red and white blood-corpuscles. There is also an account on pages 687 and 688 of the numbers of blood-corpuscles in man after extirpation of the spleen.

red are formed from the white corpuscles. Moreover some observers have described in the splenic pulp nucleated red blood-corpuscles similar to those in embryonic tissue. It might be assumed that these nucleated red blood-corpuscles formed the intermediate steps in the conversion of white into the non-nucleated red corpuscles. Miescher's observation[1] that the spleen is richer in hemoglobin than the blood deserves our notice. This author, adopting Hüfner's method, found that the salmon had twice as much hemoglobin in the spleen as in the blood.

We have now to consider whether the transitory character of the disturbances in the blood formation, which appear after excision of the spleen, may not be accounted for by the fact that other organs of the body may take up the splenic functions. It is often stated that the lymphatic glands swell after removal of the spleen. This is however by no means a constant phenomenon, and was absent, for example, in a number of experiments of this description carried out by Vulpius[2] in rabbits and goats. Swelling of the lymphatic glands has often been observed in man as a result of excision of the spleen. In this case however it is doubtful whether this change should rather be ascribed to the disease which necessitated the operation.

It seems to me more probable that the duties of the spleen are fulfilled by another tissue, *viz.*, the red marrow of bones. In 1869 Neumann[3] and Bizzozero[4] showed that the red marrow of the flat bones, the bodies of the vertebræ, and the proximal epiphyses of the bones of the limbs in mammals contained nucleated cells tinged with hemoglobin, resembling in every respect embryonic red blood-corpuscles. It is thought that these cells are formed from leucocytes and, multiplying by cell-division, are converted into non-nucleated red blood discs. The red bone-marrow presents one striking similarity to the splenic tissue, in that the veins appear to lose their proper wall, thus allowing the blood to come into immediate contact with the tissue-cells.[5] It seems therefore a likely hypothesis that the red bone-marrow should be able to take up the functions of the

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[1] Miescher, Du Bois' *Arch.*, Anat. Abth., p. 212: 1881.

[2] Vulpius, *loc. cit.*, p. 694, contains full references to previous work on the subject.

[3] E. Neumann, *Arch. d. Heilkunde*, Jahrgang x. p. 68: 1869; Virchow's *Arch.*, vol. cxix. p. 385: 1890.

[4] Bizzozero, "Sul midollo delle ossa," Napoli: 1869.

[5] Hoyer, *Med. Centralbl.*, Nos. 16 and 17: 1869; G. E. Rindfleisch, *Arch. f. mikr. Anat.*, vol. vii. p. 1: 1880.

spleen when this organ was removed. Thus P. Emelianow[1] found in the red marrow, after extirpation of the spleen in dogs, an increase of leucocytes containing hemoglobin, as well as of the transition-forms between these and the red blood-corpuscles. The observations of Pouchet[2] show however that the harmlessness of this operation does not depend on changes in the red marrow, since the spleen may be removed in the fish which have no bone-marrow without causing any alteration in the composition of their blood.

A number of cases are on record in which the spleen has been excised in man. In some instances this was rendered necessary by the prolapse of the organ through a wound in the abdominal wall. Many such cases have recovered even in the pre-antiseptic days. Morgagni[3] records the case of a woman in whom a prolapsed spleen was removed, and who lived for five years afterwards and bore children. In 1678 a Colburg surgeon, Nicolaus Matthia, extirpated the spleen of a young man which had prolapsed in consequence of a dagger wound of the abdomen. The patient lived at least six years after the operation, went about his ordinary occupations, and begat children.[4]

Encouraged by these results, surgeons have tried the effect of excising spleens in diseased conditions, such as hypertrophy, sarcoma, hydatid cysts, floating spleen, etc. In the days before asepsis and antisepsis were practiced, a violent dispute arose as to whether such a bold operation was justifiable. We may refer our readers to the treatises, which appeared in 1855 on the occasion of Küchler's operation.[5] This surgeon had ventured to remove a spleen in a man suffering from hypertrophy in consequence of malaria, and had lost his patient. On this account he was violently attacked by many of his colleagues and especially by Gustav Simon,[6] a surgeon in Heidelberg; and as vigorously defended by G. Adelmann,[7] a

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[1] P. Emelianow, *Arch. d. Sciences biolog.*, St. Pétersbourg, vol. ii. p. 135: 1893. The earlier literature is here quoted.

[2] Pouchet, *Gaz. méd. d. Paris*, p. 316: 1878.

[3] Morgagni, "De sedibus et caus. morbor," lib. v. epist. 65, art. 10, p. 368: Patavii, 1765.

[4] "Ephemerides Medic. Physic. Natur. Curiosor," Decuria ii. Ann. ii. (1684), p. 378: Norimb. 1685.

[5] H. Küchler, "Exstirpation eines Milztumors; wissenschaftliche Beleuchtung der Frage über Exstirpation der Milz bei dem Menschen," &c., Darmstadt: 1855.

[6] G. Simon, "Die Exstirpation der Milz am Menschen nach dem jetzigen Standpunkte der Wissenschaft beurtheilt," Giessen: 1857.

[7] G. Adelmann, Bemerkungen zu Dr. Küchler's Schrift: "Exstirpation eines Milztumors," *Deutsche Klinik*, Nos. 17 and 18, pp. 175 and 183: 1856, contains a critical account of all the earlier works on the extirpation of the spleen.

surgeon of Dorpat. Since aseptic precautions have been brought to perfection, removal of the spleen has become much more frequent and has been attended with more and more favorable results. In those cases which do not succeed the failure should probably hardly ever be ascribed to the loss of the splenic function. Of course in such operations it is difficult to say whether death, if it ensues, is due to the consequences of the disease or to the absence of the organ. In the cases which survive the operation unfortunately no record is usually kept of the length of the subsequent life. In 1876 however, Péan[1] showed a woman at the Parisian Académie de Médecine whose spleen had been excised ten years previously, in consequence of cystic degeneration, and who had remained throughout that time in excellent health. Vulpius[2] records the case from Czerny's clinique in Heidelberg of a woman in whom a hypertrophied floating spleen was extirpated. The patient recovered slowly, apparently because, in addition to hypertrophy, she suffered from severe nervous troubles and attacks of hysteria. Fifteen years after the operation however, she still enjoyed moderately good health. The nervous symptoms had abated, and the blooming color on her cheeks showed that there was no disturbance in her blood formation. In the first few years after the operation there had been some swelling of the inguinal and cervical glands, but this had gradually disappeared.

In certain cases of enlarged spleen, such as leukemia and lardaceous disease, other organs—liver, lymphatic glands, kidneys—are usually affected at the same time; and therefore no cure can result from removal of the spleen. Idiopathic tumors of the spleen rarely occur, but here again the blood is in an abnormal condition, as shown by the existence of anemia, leucocytosis, etc. Better results might be anticipated from this operation in cystic disease, *e. g.*, hydatids, but here a partial resection is usually sufficient. Extirpation is also indicated in cases of floating spleen, where this organ, especially if it be hypertrophied, sinks occasionally into the pelvis and produces painful stretching of the duodenum and stomach, strangulation of the blood-vessels, disturbances in digestion and nutrition, &c.

In 1893 A. Dandolo[3] collected all the cases in which excision of the spleen had been performed.

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[1] Péan, *Bulletin de l'Acad. de Méd.*, No. 29 : 1876.

[2] Vulpius, *Beitr. z. klin. Chir.*, vol. xi., pp. 638–641 : 1894.

[3] Dandolo, *Gazz. med. lombarda*, Nos. 7–9 : 1893.

	Cases.	Cure.	Death.
Floating spleen	17	15	2
Suppuration	2	2	—
Simple cysts	4	4	—
Hydatid cysts	4	3	1
Amyloid spleen	1	—	1
Fibroma	1	—	1
Sarcoma	2	1	1
Lympho-sarcoma	2	2	—
Venous engorgement	3	—	3
Simple hypertrophy	18	7	11
Malarial hypertrophy	23	12	11
Leukemia and pseudo-leukemia	25	—	25
	102	46	56

In 1894 O. Vulpius[1] published a list of 117 extirpations, 50.4 per cent. of which resulted in cure, 49.6 in death.

	Cases.	Cure.	Death.
Leukemia	28	3[2]	25
Simple and malarial hypertrophy and floating spleen	66	42	24
Hydatid	5	3	2
Simple cysts	4	4	—
Sarcoma	4	3	1
Suppuration	3	3	—
Venous congestion	3	—	3
Amyloid	1	—	1
Syphilis	1	1	—
Rupture	2	—	2
	117	59 (50.4%)	58 (49.6%)

As regards the operations for enlargement of the spleen in leukemia, again only one is reported by Vulpius to have resulted in a permanent cure, and even in this case there was some doubt as to the diagnosis. If we deduct the cases of leukemia, heart and amyloid disease, in which the patients certainly did not die from the effects of the excision, but from the original incurable disease, there remain fifty-six cures in eighty-five cases, *i. e.*, 65.9 per cent., or two-thirds of all the cases.

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[1] O. Vulpius, *Beitr. z. klin. Chir.*, vol. xi. p. 655: 1894.

[2] Only one was permanent.

Since therefore we learn from innumerable experiments on man and animals that the absence of the splenic functions does not endanger the life and health of the individual, the suggestion occurs that the functions of this organ may have some connection with the sexual functions. So far as we are aware, all the functions of our body serve directly or indirectly two purposes only: the preservation of the individual and the maintenance of the race. It would be interesting to know whether the persons whose spleen has been removed show any alteration in their sexual life. As regards animals, the following observation of Miescher's[1] is in favor of some such connection between the splenic and sexual functions. Miescher noticed that the size of the spleen varied greatly in the Rhine salmon, and that this difference in its volume depended upon the increase or diminution of the blood in it. The swollen spleen of a salmon contained sometimes one-fourth, sometimes even as much as one-half of the total blood. In the female this repletion occurs pretty regularly at certain definite seasons in the year: the spleen is at its smallest two months before (September and October) and during the period of spawning (November); and swells up after this time. In the male no such regularity could be attested; although the spleen was again at its smallest in November during the time of spawning. It appears that the spleen regulates the amount of blood in the other organs, as well as the processes of oxidation and other metabolic phenomena, thereby indirectly acting upon the development of the ovaries and testes. A similar connection between pairing time and the size of the spleen and the amount of blood in that organ was observed by A. Leonard Gaule in frogs.[2]

The relation of the splenic to the sexual functions cannot however be of very great importance, as may be inferred from the fact mentioned above that both man and animals retain their powers of propagation after removal of the spleen (compare p. 232).

Since therefore the spleen is not essential in the normal organism either to the maintenance of the individual or of the species, we must finally inquire whether it may not have a significance in abnormal conditions. It has been regarded as a means of protection against injurious substances and infective germs, which have entered the blood. This supposition appeared to be confirmed by the fact that in many infectious diseases the spleen swells. This phenomenon seems

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[1] F. Miescher-Rüsch, Du Bois' *Arch.*, Anat. Abth., p. 193: 1881.

[2] A. Leonard Gaule, *Journ. Morphol.*, vol. viii. p. 403: 1893.

to be analogous to the swelling of the lymph-glands, which evidently has the object of retaining and rendering innocuous the poison which has been absorbed. It is possible that spleenless animals would be more readily infected, and when infected, more seriously ill than normal animals. Observations on man are urgently needed as to how those persons whose spleen has been removed, withstand the infectious diseases which they may subsequently acquire. Such observations, so far as I know, have never been carried out, but the patients have, as a general rule, been completely lost sight of.

To the THYMUS has been ascribed functions similar to those of the spleen, the bone-marrow, and the lymphatic glands. In its histological aspect the thymus displays its close relation to the lymphoid organs. Besides leucocytes it contains nucleated red blood-corpuscles.[1] We must therefore assume that the red blood-cells are formed here as well as the leucocytes. But in warm-blooded animals however this function is confined to the embryonic period, until the true lymph-glands are developed. Later on it undergoes retrograde changes, and in the adult has almost completely disappeared. That the thymus takes no further part in extra-uterine life is apparent from the experiments of Von Braunschweig.[2] This observer remarked that after bleeding or removal of the spleen, the thymus underwent no change either in quite young or in full-grown animals; no increase of cell division was observed; the number of karyomitoses did not rise above the normal.

In cold-blooded animals such as the frog, the thymus persists throughout life. In these instances it is a double organ. In the frog it is situated under the depressor mandibule muscle, which becomes visible when the skin behind the tympanum and the angle of the jaw is removed. According to Abelous and Billard,[3] in the frog excision of the thymus on both sides invariably causes death three to fourteen days afterwards, with the accompaniment of paralytic symptoms, a tendency to ulceration, hydremic consistency of the blood and hemorrhages. Removal of one thymus however does not prove fatal in a healthy frog; the only difference is that such an animal tires more readily than a normal frog.

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[1] J. Schaffer, *Med. Centralblatt*, pp. 401 and 417: 1891; and *Sitzungsber. der Wiener Akad. d. Wissensch.* Math-natur. Kl., vol. cii. p. 336: 1894.

[2] R. von Braunschweig, "Exper. Unters. üb. d. Verhalten der Thymus bei der Regeneration der Blutkörperchen," Diss. Dorpat: 1891.

[3] Abelous et Billard, *Arch. d. Physiol.*, 5 (viii.), p. 898: 1896.

LECTURE XVII

GASES OF THE BLOOD AND RESPIRATION—BEHAVIOR OF OXYGEN IN THE PROCESSES OF EXTERNAL AND INTERNAL RESPIRATION

In our remarks on the composition of blood, no account has been given of its gaseous constituents. Three gases can be pumped out of blood:[1] oxygen, carbonic acid, and nitrogen.

The amount of nitrogen is inconsiderable; it does not occur here in larger quantities than it does in watery fluids which come into contact with atmospheric air. Nitrogen is simply absorbed by the blood,[2] and it appears to take no part in vital processes.[3]

The two other gases, on the other hand, are of great physiological importance: oxygen is, as we have seen, an essential food-stuff, the most potent source of energy; carbonic acid is one of the end-products of metabolism, the compound in which the bulk of the carbon leaves the animal body.

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[1] A diagram and description of the apparatus used for pumping out the gases—the gas-pump of Ludwig and of Pflüger—are given in every text-book of general physiology. As I assume that all my readers possess such a work, I shall not describe it here. The original description and diagram of the gas-pump, with which most of the experiments on the blood-gases were carried out in Ludwig's laboratory, will be found in Alexander Schmidt's paper in *Berichte über die Verhandl. d. k. sächsischen Ges. d. Wissensch. zu Leipzig*, Math. physik. Classe, vol. xix. p. 30: 1867; and the description of the apparatus constructed by Geissler and Pflüger in Pflüger's "Untersuchungen aus dem physiologischen Laboratorium zu Bonn," p. 183: Berlin, 1865. For the methods of gas-analysis, *vide* Bunsen, "Gasometrische Methoden," Braunschweig, 2d edit.: 1877; and J. Geppert, "Die Gasanalyse und ihre physiologische Anwendung nach verbesserten Methoden": Berlin, 1866.

[2] A knowledge of the laws that govern the absorption of gases is essential for the comprehension of the respiratory processes. The beginner who is not thoroughly conversant with Dalton's law, the meaning of coefficient of absorption, partial pressure, &c., must study a text-book of physics before proceeding with this and the following lectures.

[3] The theory that a small part of the nitrogen issues as a free element from the decomposition and oxidation of the nitrogenous food-stuffs in the animal body, has been upheld by some until quite recently, but has never been confirmed by accurate experiment. For this tedious contest, *vide* Pettenkofer and Voit, *Zeitschr. f. Biolog.*, vol. xvi. p. 508: 1880; Seegen and Norwak, Pflüger's *Arch.*, vol. xxv. p. 383: 1881; Hans Leo, Pflüger's *Arch.*, vol. xxvi. p. 218: 1881; J. Reiset, *Compt. rend.*, vol. xcvi. p. 549: 1883. The earlier literature is quoted in these works.

The absorption of oxygen and the excretion of carbonic acid take place among the lower animals over the whole surface of the body; among the higher animals, principally or exclusively in differentiated organs, such as lungs, gills, and tracheæ. This process is termed external, as distinguished from internal, respiration, which last term we apply to the consumption of oxygen and the formation of carbonic acid in the tissues. A few authors understand by this latter term, however, only the physical process of the interchange of gases through the walls of the blood-capillaries (the diffusion of carbonic acid from the tissues into the blood, and of oxygen from the blood into the tissues), and not the chemical processes of oxidation, of the assimilation of oxygen and the formation of carbonic acid in the tissue cells. Venous blood is rendered arterial by the process of external respiration; arterial blood venous by that of internal respiration.

As the skin and the lungs are also tissues requiring oxygen for the performance of their functions, the process of internal respiration goes on at the same time along with that of external respiration—the latter preponderating in the lung. For this reason the pulmonary vein carries arterial blood to the heart. The former process preponderates in the skin of most animals, and the blood contained in the cutaneous veins is therefore venous.

We will now consider more closely the behavior of the oxygen and carbonic acid in the processes of external and internal respiration. Let us first take OXYGEN.

Arterial dog's blood, which has served for most of the analyses on the gases of blood,[1] contains in 100 vols. from 19 to 25 vols. of oxygen, computed at 0° C., and 760 mm. Hg. The amount of oxygen in the arterial blood of herbivora (sheep, rabbit) is found to be smaller, *viz.*, from 10 to 15 volumes per cent.[2]

This amount of oxygen is far too large to remain merely absorbed in the blood. One hundred volumes of water absorb 4 vols. of oxygen at 0° C. from an atmosphere of pure oxygen; and from the ordinary atmosphere, in which the tension of the oxygen is five times less, it would therefore absorb less than 1 vol. of oxygen, and at the temperature of the body even still less. Watery solutions also absorb less than pure water; a large proportion of the 10 to 25 vols. of oxygen in arterial

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[1] Pflüger, *Centralbl. f. d. med. Wissensch.*, p. 722: 1867; and Pflüger's *Arch.*, vol. i. p. 288: 1868. The previous analyses are also given here.

[2] Sczelkow, Du Bois' *Arch.*, p. 516: 1864; Preyer, *Wiener med. Jahrber.*, p. 145: 1865; Fr. Walter, *Arch. f. exper. Path. u. Pharm.*, vol. vii. p. 148: 1877.

blood must therefore be chemically combined.[1] We know, in fact, that it is the hemoglobin which serves for this loose combination.[2] This is shown by the fact that a pure solution of hemoglobin, containing the same amount of hemoglobin as the blood, combines with as much oxygen and gives off as much *in vacuo* as the blood does. The larger proportion of oxygen in dog's blood than in the blood of herbivora is explained by the fact that the former is endowed with a larger amount of blood-corpuscles and of hemoglobin. The amount of hemoglobin, and therefore of oxygen, is much less considerable in the blood of cold-blooded than in that of warm-blooded animals.

The compound of oxygen with hemoglobin, or 'oxyhemoglobin,' is well known to be of a lighter color than reduced hemoglobin, and shows different lines of absorption in the spectrum. The bright red coloring of arterial, and the dark red tint of venous, blood depend upon this fact.

If oxygen is chemically combined with hemoglobin, we should expect them to be combined in molecular proportions. It would be interesting to ascertain how many atoms of oxygen go to one atom of iron. The analyses made up to the present time are not exact enough for this purpose; they show however that about 2 or 3 atoms of oxygen correspond to 1 atom of iron.[3] The figures, so far, only demonstrate that there is at least four times as much oxygen taken up in the transition of hemoglobin into oxyhemoglobin, as there is in the transition from suboxid to oxid of iron, or from ferrocyanid to ferricyanid of potassium. Possibly the sulphur of the hemoglobin also plays a part in the loose oxygen compound, and a similar part may be assigned to the sulphur atoms in all proteids. It is noteworthy that, according to previous analyses, the animals that require more oxygen (compare Lecture XIII.) have likewise more sulphur in their hemoglobin. Four atoms of sulphur in the hemoglobin of the horse, six in that of the dog, and nine in that of the hen, go to two atoms of iron.[4] Is this an accidental correspondence?

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[1] Liebig in his *Ann. d. Chem. u. Pharm.*, vol. lxxix. p. 112: 1851; Lothar Meyer, "Die Gase des Blutes," Dissert.: Göttingen, 1857; also Henle and Pfeufer's *Zeitschr. f. rat. Med.*, N. F., vol. xviii. p. 256: 1857.

[2] Hoppe-Seyler, *Arch. f. path. Anat.*, vol. xxix. p. 598: 1864; and *Med. chem. Unters.*, p. 191: 1867.

[3] Hüfner, *Zeitschr. f. physiol. Chem.*, vol. i. pp. 317, 386: 1877; vol. iii. p. 1: 1880. John Marshall, *Zeitschr. f. physiol. Chem.*, vol. vii. p. 81: 1883. Hüfner, *Zeitschr. f. physiol. Chem.*, vol. viii. p. 358: 1884. The previous determinations are quoted here. Compare also Hoppe-Seyler, *ibid.*, vol. xiii. p. 477: 1889. G. Hüfner, Du Bois' *Arch.*, p. 130: 1894.

[4] A. Jaquet, "Beitr. zur Kenntniss des Blutfarbstoffes," Dissert.: Basel, 1889.

The oxygen in loose combination with the hemoglobin may be displaced by an equal volume of carbonic oxid,[1] or of nitric oxid,[2] a fact which likewise speaks for the chemical union of the oxygen.

It may be objected that the oxyhemoglobin combination could hardly be destroyed by a mere vacuum, if it were really a chemical compound. But, as a matter of fact, it is not the vacuum which splits up the oxyhemoglobin, but the heat. A solution of oxyhemoglobin may be evaporated to dryness at a very low temperature, *i. e.*, below 0° C. *in vacuo;* the oxyhemoglobin crystals are not affected. The higher the temperature, the greater must be the pressure of oxygen in order to counterbalance the dissociating force of heat. The affinity of a substance increases in proportion to the number of atoms which coöperate in the attraction, or in proportion to the number of atoms in the unit of volume. This phenomenon is called the influence of mass.[3] Two antagonistic forces are at work in the formation and decomposition of oxyhemoglobin: heat endeavors to separate, chemical affinity seeks to unite. Affinity increases with the influence of mass, with the density, with the partial pressure of the oxygen. The vacuum therefore acts only by reducing the mass-influence of the oxygen to a minimum, and thus enabling the antagonistic heat to attain supremacy.

I may here remind my readers of an analogous phenomenon well known in inorganic chemistry. When chalk is burnt, the carbonic acid is separated from the lime by heat. But this separation does not take place in an atmosphere of pure carbonic acid; on the contrary, quicklime unites with CO_2 at a high temperature, if the partial pressure of the carbonic acid be sufficient. If the carbonate of lime is to be rapidly converted into quicklime, a stream of another gas must be passed over it, so as to reduce the partial pressure of the carbonic acid. The same thing takes place in the relation of hemoglobin to oxygen.

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[1] Cl. Bernard, "Leçons sur les effets des substances toxiques," &c.: Paris, 1857; Hoppe-Seyler, Virchow's *Arch.*, vol. xi. p. 288: 1857; and vol. xxix. pp. 233, 597: 1863; Lothar Meyer, "De Sanguine oxydocarbonico infecto," Dissert. Vratislaviæ: 1858; Hoppe-Seyler, *Med. chem. Unters.*, p. 201: 1867; *Zeitschr. f. physiol. Chem.*, vol. 1, p. 131: 1877; John Marshall, *Zeitschr. f. physiol. Chem.*, vol. vii. p. 81: 1883; R. Külz, *ibid.*, p. 384; G. Hüfner, *Journ. f. prakt. Chem.*, N. F., vol. xxx. p. 67: 1884.

[2] L. Hermann, Du Bois' *Arch.*, p. 469: 1865; Hoppe-Seyler, *Med. chem. Unters.*, p. 204: 1867; W. Preyer, "Die Blutkrystalle," p. 144: Jena, 1871; Podolinski, Pflüger's *Arch.*, vol. vi. p. 553: 1872.

[3] For the explanation of the phenomenon of the influence of mass, afforded by the mechanical theory of heat, see Lothar Meyer, "Die modernen Theorien der Chemie," 5th edit., p. 479: Breslau, 1884, or "Lehrbuch der allgemeinen Chemie," by W. Ostwald, vol. ii. part ii.: Leipzig, 1887.

In the alveoli of the lungs, where the partial pressure of the oxygen is considerable, the hemoglobin is completely or very nearly saturated with oxygen. In the capillaries of the tissues, where the oxygen that has been simply absorbed diffuses itself or enters into combination with reducing substances, so that the partial pressure diminishes, a portion of the combined oxygen is at once set free by the liberating force of heat, and the partial pressure of the oxygen rises again till it balances the effect of the heat. In this way, the red blood-corpuscle is always surrounded by oxygen under a definite pressure.

This arrangement serves a double purpose. Firstly, there is far more oxygen brought to each tissue by the blood-current in a definite period than would be possible by simple absorption of the oxygen without chemical combination. The processes of oxidation might go on much more rapidly, and yet there would not be a scarcity of oxygen. The amount of oxygen in the plasma is very little less when the oxygen is lavishly used up than when it is economically expended. The store of oxygen in the capillaries is never exhausted under normal conditions. In venous blood, at least 5 per cent. by volume of oxygen is always found, and generally far more. Only in asphyxial blood does the oxygen almost entirely disappear.[1]

Secondly, the chemical combination of oxygen offers the great advantage that the intensity of the processes of oxidation is, to a great extent, independent of the partial pressure of the oxygen in the surrounding media. Direct experiment has shown that the partial pressure of the oxygen in the surrounding atmosphere may increase threefold or diminish to one-half without any disturbance being manifested in the breathing of a mammal.[2]

When the partial pressure is reduced still further, the frequency of respiration increases; and when it sinks to 3.5 per cent. of an atmosphere, the animals die.[3]

Fraenkel and Geppert[4] allowed dogs to breathe rarefied atmospheric air, and analyzed the gases of their arterial blood.

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[1] N. Stroganow, Pflüger's *Arch.*, vol. xii. p. 22 : 1876. The previous experiments on the blood of asphyxiated animals are quoted here.

[2] Wilh. Müller, *Ann. d. Chem. u. Pharm.*, vol. cviii. p. 257 : 1858. Paul Bert, "La pression barométrique": Paris, 1878. A. Fraenkel and J. Geppert, "Ueber die Wirkungen der verdünnten Luft auf den Organismus": Berlin, Hirschwald, 1883. *Vide* also L. de Saint Martin, *Compt. rend.*, vol. xcviii. p. 241 : 1884; and S. Lukjanow, *Zeitschr. f. physiol. Chem.*, vol. viii. p. 313 : 1884.

[3] N. Stroganow, Pflüger's *Arch.*, vol. xii. p. 31 : 1876. An account of former work is given here.

[4] Fraenkel and Geppert, *loc. cit.*, p. 47. The experiments similar to those of Paul Bert are also critically discussed here.

They found that when the pressure of air sank to 410 mm. Hg. the normal amount of oxygen was retained in the arterial blood. If the pressure of air sank to between 378 and 365 mm. Hg., or to half an atmosphere, the amount of oxygen in the arterial blood was somewhat diminished. But it was not until the atmospheric pressure sank below 300 mm. that a considerable decrease of oxygen was observed.

The partial pressure of oxygen might *à priori* have been thought to exercise a much slighter influence than we have shown it to possess; for, according to the experiments of Worm Müller,[1] the blood outside the body becomes almost completely saturated with oxygen on being shaken with atmospheric air of only 75 mm. Hg. But these experiments were carried out at the temperature of the room. At the temperature of the body, decomposition of the oxyhemoglobin begins at a higher partial pressure, as Paul Bert[2] and Fraenkel and Geppert[3] have shown. And besides it must be remembered that, in the lungs, oxygen at a low tension cannot be diffused through the walls of the alveoli rapidly enough to saturate each blood-corpuscle during its short transit through the capillaries.

The experience obtained in mountain and balloon ascents is in complete harmony with the results of the experiments on animals.[4] Real dyspnea does not begin till a height of 5000 meters is reached, which corresponds to a mercurial pressure of 400 mms. Human beings and animals live as well on the high plateaus of the Andes at 4000 meters above the level of the sea as on the sea-coast.

The poisonous influence of carbonic oxid depends perhaps only on the displacement of the oxygen. J. Haldane[5] found that the poisonous effect was smaller, the greater the partial pressure of the oxygen. If the oxygen pressure amounted to two atmospheres, the carbonic oxid pressure could be raised to as much as one atmosphere, without any inconvenience to the animal. Animals devoid of hemoglobin (*e. g.*, black-beetles), are not influenced in the slightest degree by the presence of carbonic oxid in the air.

We must now ask in what organs and tissues of our bodies the oxygen gets used up.

Lavoisier, who first recognized the importance of oxygen in vital processes, thought that combustion occurred exclusively

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[1] Worm Müller, *Ber. d. sächs. Ges.*, vol. xxii. p. 351: 1870.

[2] Paul Bert, "La pression barométrique," p. 691.

[3] Fraenkel and Geppert, "Ueber die Wirkungen der verdünnten Luft auf den Organismus," p. 57.

[4] Paul Bert, *loc. cit.*, gives an interesting account of these experiences.

[5] J. Haldane, *Journ. of Physiol.*, vol. xviii. p. 201: 1895.

in the lung. It was not until Magnus[1] had analyzed the gases of the blood that it was proved that oxygen passes on to the capillaries, and there partially disappears. But the question as to whether the processes of oxidation are completed only within the closed blood-current, or whether free oxygen is diffused through the walls of the capillaries into the tissues, has not yet been decided.

The former theory, *i. e.*, that the oxygen is consumed within the blood-vessels, has found supporters even up to the present time. The most obvious objection to it is that kinetic energy is liberated in the tissues, and particularly in the muscles, and that the most fertile source of energy lies in the affinity of oxygen for the substances of nutrition. But, on the other hand, we know that there is stored up in food a considerable amount of chemical potential energy, which is converted into kinetic energy by the mere decomposition of the food-stuffs, without any oxidation taking place (compare Lectures X. and XXIII.). The amount of this potential energy is not exactly known; it must be admitted that it may be sufficient to perform the work of muscle, and that the products of decomposition thus formed may diffuse into the capillaries, to be there oxidized, and then to serve as sources of bodily heat.

This view appeared to receive confirmation from the following experiment of Ludwig and Alexander Schmidt.[2] It has already been mentioned that the blood of animals which have died from suffocation contains only traces of oxygen, and sometimes none at all. If oxygen be added to such blood outside the body, a part of the oxygen thus artificially introduced rapidly disappears, and the carbonic acid is increased. The blood from asphyxiated animals contains substances that are readily oxidized. The blood of other animals also combines with some oxygen outside the body,[3] but the oxygen absorbed is much less in amount and disappears much more slowly than in the case of the blood from asphyxiated animals.[4] Ludwig and Alexander Schmidt explain these facts thus: Under normal conditions, readily oxidized compounds are continually finding their way from the tissues into the capillaries, where they are immediately decomposed by the free oxygen, so that they cannot be traced in normal blood. In asphyxiated animals, on the other

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[1] G. Magnus, *Ann. d. Physik*, vol. xl. p. 583: 1837; and vol. lxiv. p. 177: 1845.

[2] Alex. Schmidt, *Ber. über die Verhandl. der sachs. Ges. der Wissensch. zu Leipzig*, Math. phys. Classe, vol. xix. p. 99: 1867. *Vide* also N. Stroganow, Pflüger's *Arch.*, vol. xii. p. 41: 1876.

[3] Pflüger, *Centralbl. f. d. med. Wissensch.*, pp. 321, 722: 1867.

[4] Alex. Schmidt, *loc. cit.*, p. 108.

hand, they remain stored up in the blood in consequence of the absence of oxygen. According to the laws which govern the diffusion of gases, we should expect to find that the oxygen in the blood would penetrate the liquids of all the tissues. It is however conceivable that the oxygen may be hindered from doing so by the reducing substances which, flowing unintermittently from the tissues into the blood, meet the oxygen on its way and prevent its advance beyond the capillary wall.

The opposite view, that oxidation takes place in the other tissues as well,[1] rests upon the following facts of comparative physiology.[2] It is well known that nearly all the lower animals which have no blood, die at once without oxygen, and that this source of energy is indispensable to every cell.[3] The vegetable cell has likewise essentially the same metabolism, and cannot live without free oxygen. The higher animals, with a differentiated system of blood-vessels, require oxygen in the first stages of existence, even before the formation of blood-corpuscles, as the respiration of a bird's egg shows.[4]

Nevertheless we cannot admit that these facts afford indubitable proof of respiration in the tissues of the higher animals when fully developed; for the essence of the higher organization consists in the fact that there is, synchronous with the differentiation of the tissues and organs, a division of labor. It is quite conceivable that decomposition and oxidation may take place in the same cell among the lower animals only, and that in the more highly organized ones the duty of oxidation is exclusively relegated to the blood, the processes of decomposition going on in the other tissues.

But it can be shown that oxidation also occurs in the tissues of insects, which possess a vascular system although not so highly developed as the vertebrata. This is proved by the fact that the finest branches of a trachea run down as far as the individual cells of the tissue.[5] The observations made

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[1] The first decided advocate of this view was, so far as I know, Moritz Traube, Virchow's *Arch.*, vol. xxi. p. 386: 1861.

[2] Pflüger, in his *Arch.*, vol. x. p. 270: 1875.

[3] It is still a matter of controversy whether certain organisms of the lowest kind—yeast-cells, certain bacteria—can live entirely without free oxygen, "anaërobic." It appears however that this question may now be answered in the affirmative. *Vide* J. W. Gunning, *Journ. f. prakt. Chem.*, vol. xvi. p. 314: 1877; vol. xvii. p. 266: 1878; and vol. xx. p. 434: 1879; Nencki, *Journ. f. prakt. Chem.*, vol. xix. p. 337: 1879; Br. Lachowicz und Nencki, Pflüger's *Arch.*, vol. xxxiii. p. 1: 1883; and Nencki, Pflüger's *Arch.*, vol. xxxiii. p. 10: 1883. Compare also G. Bunge, "Ueber das Sauerstoffbedürfniss der Darmparasiten," *Zeitschr. f. physiol. Chem.*, vol. viii. p. 48: 1883.

[4] J. Baumgärtner, "Der Athmungsprocess im Ei," Freiburg i. B.: 1861.

[5] Kupffer, "Beiträge zur Anatomie und Physiologie, als Festgabe C. Ludwig gewidmet von seinen Schülern," p. 67: 1875; Finkler, Pflüger's *Arch.*, vol. x. p. 273: 1875.

by Max Schultze[1] on the *Lampyris splendidula* are particularly conclusive. In the glow organs of this animal certain cells adhere to the tracheal endings, "like the flowerets of an umbelliferous plant." These cells, as well as the tracheal endings, stain a deep black with osmic acid, owing to the separation of the metallic osmium; consequently there is present in these cells a substance with a powerful attraction for oxygen. It may therefore readily be supposed that this substance, by combining with the oxygen introduced through the tracheæ, brings about the development of light. The illuminating power of the paired glow organs continues after they have been isolated, and even after a microscopic section has been made. Max Schultze observed under the microscope that "with the rhythmic increase and diminution of the light, which these animals generally exhibit distinctly, the first appearance of the light is characterized by minute coruscations in the glow organ, which correspond in number and arrangement to the terminal cells of the tracheæ." When the oxygen is withdrawn, the illuminating power ceases.[2] Max Schultze also remarks that the tracheal terminations in other organs, as well as those in the glow organs, are rapidly stained black if the animals be placed alive in osmic acid.

In view of these facts, it cannot be doubted that free oxygen is used up in the tissues of insects. A critical observer will nevertheless hesitate before applying these results to the vertebrata. In the case of the latter, it is only in the placenta of mammals and in the salivary glands that the oxygen has been definitely proved to make its way out through the capillary walls.

The blood of the umbilical vein is of a brighter red than that of the umbilical arteries, and oxyhemoglobin can be traced in the former by the spectroscope.[3] It is well known that the blood-vessels of the mother and of the embryo do not communicate in the placenta; they form two separate capillary systems. The oxygen must therefore be first diffused through the capillary walls of the mother's vascular system, and then through those of the fetus, before reaching the blood of the latter.

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[1] Max Schultze, *Arch. f. mik. Anat.*, vol. i. p. 124: 1865.

[2] An interesting account of the numerous observations on the illuminating power of various animals, and its dependence on the presence of oxygen, is given by Milne Edwards, "Leçons sur la physiologie et l'anatomie comparée," vol. viii. pp. 93–120: Paris, 1863; and by Pflüger, in his *Arch. f. d. ges. Phys.*, vol. x. pp. 275–300: 1875. For the experiments on the chemical side, *vide* Radziszewski, *Ber. d. deutsch. chem. Ges.*, vol. xvi. p. 597: 1883, where the previous writings on this subject are quoted.

[3] Zweifel, *Arch. f. Gynäkologie*, vol. ix. p. 291: 1876; Zuntz, Pflüger's *Arch.*, vol. xiv. p. 605: 1877.

That oxygen passes through the capillary wall in the salivary glands is apparent, for the simple reason that the saliva contains free oxygen. So large an amount of oxygen passes out of the blood therefore, that the cells of the glandular tissue cannot consume it, and the excess escapes with the secretion. Pflüger[1] ascertained the presence of absorbed oxygen in the submaxillary secretion with the aid of the gas-pump; he found that it amounted to from 0.4 to 0.6 per cent. of the volume of the saliva. This fact was confirmed by Hoppe-Seyler, who used a very sensitive test for free oxygen, a hemoglobin solution which, on coming into contact with fluids containing oxygen, at once shows the absorption-bands characteristic of oxyhemoglobin.[2] Hoppe-Seyler found that the secretions of both the submaxillary and of the parotid contained oxygen.

Hoppe-Seyler, on the other hand, could detect no trace of oxygen in the bile and urine with the aid of his sensitive reagent.[3] Nor has any free oxygen been found definitely in lymph. Free oxygen has therefore not been proved with certainty to exist in most organs of vertebrata.

Pflüger and Oertmann[4] founded their proof on the following experiment. They showed that a frog, in whose vascular system a solution of common salt circulated instead of blood, used up as much oxygen, and produced as much carbonic acid in an atmosphere of pure oxygen, as a normal frog would do. A fine cannula is tied into the central end of the abdominal vein[5] of a frog, and a 0.75 per cent. solution of salt injected, until increasingly diluted blood and finally pure salt solution flows from the peripheral opening of the vein.[6] Frogs thus treated generally lived one or two days. If such frogs were introduced into an atmosphere of pure oxygen, they consumed as much oxygen and developed as much carbonic acid in from

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[1] Pflüger, in his *Arch.*, vol. i. p. 686: 1868.

[2] Hoppe-Seyler, *Zeitschr. f. physiol. Chem.*, vol. i. p. 135: 1877. The apparatus used by him to admit of the action of the hemoglobin solution on the secretion, without coming in contact with the atmospheric air, is described here.

[3] The traces of oxygen which Pflüger (*Arch.*, vol. ii. p. 156: 1869) found in the gases that were pumped out of the urine, milk, and bile, were probably only due to the unavoidable contamination with atmospheric air.

[4] E. Oertmann, Pflüger's *Arch.*, vol. xv. p. 381: 1877.

[5] The work of Alex. Ecker, "Die Anatomie des Frosches," Vieweg and Sohn, 1864–1882 [translated into English by G. Haslam, Foreign Biological Memoirs; Clarendon Press, Oxford], will serve to acquaint the reader with the anatomy of the frog. It is plentifully supplied with illustrations, and contains a complete account of the literature of the subject. [A new edition of this work, edited by Gaupp, is now appearing.]

[6] This method of obtaining frogs free from blood was first introduced by Cohnheim (Virchow's *Arch.*, vol. xlv. p. 333: 1869).

ten to twenty hours as a normal animal. Oertmann concluded from this experiment that oxidation proceeded only in the tissues, because they alone used up as much oxygen as the tissues and the blood together. But this is not a necessary conclusion. The facts may equally well be interpreted in support of the opposite view. It might be argued in this case that, again, only processes of decomposition had taken place in the tissues of the 'salt-frog'; that the products of decomposition had been diffused through the capillary wall into the solution of salt containing oxygen, and had been oxidized within the closed vascular system. The partial pressure of the oxygen, being five times greater than normal, had made up for the want of hemoglobin.

In conclusion, we must however mention the following very interesting fact, ascertained by Ludwig and his pupils. Afonassiew[1] found that the reducing substances of the blood from asphyxiated animals occur only in the blood-corpuscles, and not in the serum; and Tschiriew[2] found that the lymph of such animals is also free from these substances.

It thus appears that the blood is only concerned in processes of oxidation in so far as living cells are suspended in it; that all oxidations in our body proceed exclusively in the active elements of the tissues—in the cells and the products of the metamorphosis, but not in the fluids surrounding them.

This theory is rendered so probable by all the facts and analogies of the case that it is accepted by every physiologist.

We have now to consider how the rapid and complete oxidation of the food-stuffs in our tissues is to be explained. The food eaten at the most abundant meal becomes, before six hours have elapsed, nearly all converted by oxidation into the end-products, carbonic acid, water, and urea; whereas proteid, fats, and carbohydrates are not affected by oxygen external to, and at the temperature of, the body. Other conditions favorable to oxidation must therefore be present in the body.

The most obvious suggestion was that the alkalinity of the blood, of lymph, and of protoplasm had something to do with the matter. It is known that the oxidation of organic substances proceeds more rapidly in an alkaline than in a neutral or acid solution. I may remind my readers of the behavior of pyrogallol—and, indeed, of all polyatomic phenols—of the leuco-compounds of numerous dye-stuffs, of grape-sugar, &c. The latter, dissolved in soda, absorbs oxygen rapidly at the temperature of the body. But it must be remembered that

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[1] N. Afonassiew, *Ber. d. sächs. Ges. d. Wissensch.*, vol. xxiv. p. 253: 1872.

[2] S. Tschiriew, *ibid.*, vol. xxvi. p. 116: 1874.

for this purpose free alkali is necessary, whereas our tissues contain only carbonates or possibly bicarbonates of the alkalies, since free carbonic acid penetrates all tissue elements.

Nencki and Sieber[1] have indeed shown that dilute solutions of sodium carbonate and grape-sugar or proteid also absorb oxygen. But the amount absorbed is small, and the absorption takes place very slowly. Schmiedeberg[2] showed that benzylalcohol and salicylaldehyde are not appreciably oxidized by the atmospheric air in the presence of water. If these substances were brought into contact with blood or dilute sodium carbonate solution instead of water, a small trace of the benzylalcohol was oxidized to benzoic acid. The salicylaldehyde was also under these circumstances unchanged. If however these substances were passed with oxygenated defibrinated blood through the kidneys or lungs of dogs or pigs, a considerable amount of both was oxidized to benzoic acid and salicylic acid respectively. The same result was obtained when watery extracts of these organs mixed with salicylaldehyde were exposed in thin layers to the action of the atmospheric oxygen. The quantity of salicylic acid formed however was only small. Boiling destroyed the oxidizing action of the extracts.[3] It seems to me that we cannot at present draw any conclusion as to the behavior of the food-stuffs in our body from a consideration of the changes undergone by such easily oxidizable substances.

In order to explain the rapid oxidation of food-stuffs in the body, recourse has been had to the assumption that a portion of the inspired oxygen is converted in our tissues into that powerful oxidizing modification termed ozone. Even Schönbein,[4] the discoverer of ozone, mentioned this hypothesis. What therefore is known concerning ozone?

If induced currents be allowed to pass through oxygen, condensation takes place, and the oxygen now contains ozone. A small part only of the oxygen—at most 5 per cent.—is converted into ozone. The volume of the ozone amounts to only two-thirds of that of the oxygen from which it was formed. Soret[5] has ascertained this in the following manner. Oil of turpentine absorbs only the ozone from oxygen con-

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[1] Nencki and Sieber, *Journ. f. prakt. Chem.*, vol. xxvi. p. 1: 1882.

[2] Schmiedeberg, *Arch. f. exper. Path. u. Pharm.*, vol. xiv. pp. 288 and 379: 1881. Compare also Salkowski, *Zeitschr. f. physiol. Chem.*, vol. vii. p. 155: 1882; and *Centralbl. f. d. med. Wissensch.*, p. 849: 1892.

[3] A. Jaquet, *Arch. f. exper. Path. u. Pharm.*, vol. xxix. p. 386: 1892.

[4] Schönbein, Poggendorff's *Annal.*, vol. lxv. p. 171: 1845.

[5] Soret, *Ann. Chem. Pharm.*, vol. cxxvii. p. 38: 1863; vol. cxxx. p. 95: 1863; Suppl. v. p. 148: 1867; *Compt. rend.*, vol. lvii. p. 604: 1863.

taining ozone, the amount of which is ascertained from the diminution of volume. If a sample of this oxygen containing ozone be heated, the ozone is destroyed, and the volume increases. This increase of volume is always half as much as the diminution of volume by absorption. Therefore on heating, one volume of ozone becomes one and a half volumes of oxygen, two volumes of ozone become three volumes of oxygen. It follows, both from this fact and from Avogadro's hypothesis (that equal volumes of gas contain an equal number of molecules), that ozone contains three atoms of oxygen in each molecule. Three oxygen molecules of two atoms each have produced two ozone molecules of three atoms. We may imagine that the two atoms in the oxygen molecule become separated from each other by the kinetic energy of the electric current, and each of them attaches itself loosely to an intact oxygen molecule. This third oxygen atom, thus loosely combined, has a strong affinity for oxidizable substances.[1] In fact, in oxidation by ozone, never more than a third of the weight of the ozone enters into combination, and no diminution of volume of the oxygen containing ozone occurs.

This theory is also strictly in accordance with the fact that even at a low temperature ozone oxidizes substances which ordinary oxygen does not attack except at a high temperature. In the case of ordinary oxygen, the atoms must first be separated by the kinetic energy of heat. With ozone, this was done beforehand by the kinetic energy of the electric current.

It is well known that ozone also arises as a by-product during the slow oxidation of phosphorus. An idea can be formed of this process by the following explanation: during the slow oxidation only one of the two atoms of the oxygen molecule enters into combination with the phosphorus; and the other attaches itself to an undecomposed molecule of oxygen.

It may be seen from the above that the third oxygen atom in the ozone molecule, which causes the powerful oxidations, can have no other properties than that of nascent oxygen. In fact it can be proved that wherever slow oxidation occurs, a part of the oxygen acquires 'active qualities,' and acts in the same way as the ozone formed during slow oxidation of phosphorus. We cannot expect that ozone should be formed when oxidizable substances are present, as these fix the nascent oxygen atom before it can unite with a molecule of oxygen to form one of ozone.

It is with such conditions that we have to deal in the

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[1] Clausius, Poggendorff's *Annal.*, vol. cxxi. p. 250: 1864.

organism, and for these reasons ozone is never formed in the body, though we meet with energetic processes of oxidation. *A priori* there is no point in trying to trace ozone in the animal body. Many liters of oxygen containing ozone might be introduced into the blood, and yet we could not pump out a single molecule of ozone.

The following experiments show that some of the oxygen atoms attain 'active properties' during slow oxidation by ordinary oxygen.

If ammonia be present during the oxidation of pyrogallol in alkaline solution by atmospheric oxygen, it becomes oxidized into nitrous acid.[1] Peroxid of hydrogen is formed during the oxidation of benzaldehyde.[2] If metallic sodium be oxidized by air in the presence of petroleum-ether, the hydrocarbons, which compose the latter, are converted into the corresponding alcohols and acids.[3]

It is well known that benzol cannot be converted into phenol by the action of the ordinary oxidizing agents, but that it can by means of ozone.[4] It can however be done by ordinary oxygen, if ferrous or cuprous sulphate are present.[5] We must imagine that the suboxid fixes one of the two oxygen atoms, while the one set free oxidizes the benzol.

Palladium-hydrogen has the same effect as the suboxid of iron or copper. Graham has shown that, if palladium foil be employed as the negative electrode in the electrolysis of water, no hydrogen is developed at this pole. The hydrogen unites with the palladium. The metal takes up nine hundred times its volume of the gas, while at the same time its own volume increases. This combination gradually liberates a part of the hydrogen; it behaves like nascent hydrogen. When therefore the palladium-hydrogen comes in contact with atmospheric oxygen, the hydrogen becomes oxidized, a part of the oxygen is rendered 'active,' and if benzol is present, it is converted into phenol, as it would be by ozone.[6]

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[1] This experiment of Baumann's was communicated by Hoppe-Seyler, *Ber. d. deutsch. chem. Ges.*, vol. xii. p. 1553: 1879.

[2] Radenowitsch, *Ber. d. deutsch. chem. Ges.*, p. 1208: 1873.

[3] Hoppe-Seyler, *Ber. d. deutsch. chem. Ges.*, vol. xii. pp. 1553, 1554: 1879.

[4] Nencki and P. Giacosa, *Zeitschr. f. physiol. Chem.*, vol. iv. p. 339: 1880. Leeds (*Ber. d. deutsch. chem. Ges.*, vol. xiv. p. 975: 1881) could not confirm this statement; in his experiments, the benzol was oxidized into carbonic acid, oxalic acid, formic acid, and acetic acid. But the conditions under which the experiments were carried out differed in the two cases.

[5] Nencki and Sieber, *Journ. f. prakt. Chem.*, vol. xxvi. pp. 24, 25: 1882.

[6] Hoppe-Seyler, *Zeitschr. f. physiol. Chem.*, vol. ii. p. 22: 1878; and vol. x. p. 35: 1886; *Ber. d. deutsch. chem. Ges.*, vol. xii. p. 1551: 1879; and vol. xvi. pp. 117, 1917: 1883. Compare also Leeds, *ibid.*, vol. xiv., p. 975: 1881; and Moritz Traube, *ibid.*, vol. xv. p. 659; vol. xvi. pp. 123, 1201: 1883; and vol.

Nascent oxygen, as might *à priori* be assumed, acts as a more energetic oxidizer even than ozone. Ozone, for instance, cannot oxidize free nitrogen, any more than it can carbonic oxid. The nascent oxygen, on the other hand, arising from the action of palladium-hydrogen on ordinary oxygen, oxidizes free nitrogen to nitrous acid, and carbonic oxid to carbonic acid.[1]

If benzol is introduced into our body, it mostly reappears in the urine as phenol.[2] We may therefore assume that reducing substances also occur in our tissues, and play a part similar to that taken by them in the above-mentioned experiments with palladium-hydrogen or the metallic suboxids. I have already stated (pp. 244, 247) that such reducing substances are found in the blood of asphyxiated animals; and they are moreover to be met with in all tissues. Ehrlich[3] showed that blue coloring matters, as alizarin blue, indophenol blue, lose their color in the tissues of living animals, and that the tissues turn blue again on contact with the air. We may assume that these readily oxidizable reducing substances arise by fermentative action from the food-stuffs along with other products of decomposition that are not readily oxidizable. But as soon as the readily oxidizable substances become oxidized by the inspired oxygen, a part of the oxygen attains 'active' properties, and oxidizes those which are not readily oxidizable.

That reducing substances do arise by fermentative action in the cells, may be seen in butyric acid fermentation. The hydrogen liberated in this process becomes oxidized by ordinary oxygen to form water. Hydrogen never proceeds from fermentative processes, if there has been a sufficient access of air.[4] This explains the absence of hydrogen in the atmosphere in spite of the extensive processes of fermentation going on all over the surface of the earth.

The formation of saltpeter shows us moreover in a very

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xviii. pp. 1877–1900: 1885; also Baumann and Preusse, *Zeitschr. f. physiol. Chem.*, vol. iv. p. 453: 1880; Nencki, *Journ. f. prakt. Chem.*, vol. xxiii. p. 87: 1880; and Baumann, *Zeitschr. f. physiol. Chem.*, vol. v. p. 244: 1881; and *Ber. d. deutsch. chem. Ges.*, vol. xvi. p. 2146: 1883. Moritz Traube has raised objections of considerable weight to the theory that oxygen is rendered active by reducing substances. I have given this theory in my account, but must expressly state that it may involve hypotheses and analogical inductions from facts which possibly are capable of a different interpretation. The reader may form his own judgment from the interesting and instructive works quoted above.

[1] Baumann, *Zeitschr. f. physiol. Chem.*, vol. v. p. 244: 1881.

[2] Schultzen and Naunyn, Reichert and Du Bois' *Arch.*, p. 349: 1867.

[3] P. Ehrlich, "Das Sauerstoffbedürfniss des Organismus": Berlin, 1885.

[4] Hoppe-Seyler, Pflüger's *Arch.*, vol. xii. p. 16: 1876; *Zeitschr. f. physiol. Chem.*, vol. viii. p. 214: 1884.

remarkable way, how processes of oxidation may go on in a most energetic manner at the same time as processes of decomposition produced by putrefactive organisms. Nitrogen, which has but a slight affinity for oxygen, is raised to the highest stage of oxidation by the oxygen-atoms which are liberated during the oxidation of the reducing putrefactive products and which oxidize the ammonia resulting from the decomposition. Recent researches have proved that certain living putrefactive organisms take an active part in the formation of saltpeter.[1]

It is probable that all the cells in our bodies have the same power as these unicellular beings, these organisms associated with fermentation and decomposition. But we need not assume that the reducing substances formed by them are always the same. Hoppe-Seyler[2] is of opinion that hydrogen is liberated in the tissues of the animal body just as it is in certain unicellular putrefactive organisms. That the hydrogen cannot be detected in the tissues is no argument against this view. But, however this may be, the nascent hydrogen need not be the only reducing substance by means of which active oxygen arises in our tissues. These reducing substances may be of very different kinds in the various cells; they may even be numerous and changeable in one and the same cell, according to the functions it is required to perform at a given moment.[3]

The 'spontaneous combustion' of hay affords a striking example of the activity which oxidation of the organic foodstuffs may attain when decomposition of the latter has previously set in. If hay is stacked before it is thoroughly dry, decomposition begins in the middle of the damp stack through the action of organized or unorganized ferments. As all decomposition by ferments is accompanied by hydration, drying is the best means of preventing it. Heat is liberated by the decomposition, and proportionately with the rise in temperature in the middle of the stack an ever-increasing accumulation of easily oxidizable decomposition-products is formed. If the hay be now disturbed so that there is free

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[1] Muntz et Schlösing, *Compt. rend.*, vol. lxxxiv. p. 301: 1877; vol. lxxxv. p. 1018: 1877; vol. lxxxix. p. 891: 1879; Warrington, *Chem. News*, vol. xxxvi. p. 263: 1877; vol. xxxix. p. 224: 1879; S. Winogradsky, *Compt. rend.*, vol. cx. p. 1013: 1890.

[2] Hoppe-Seyler, Pflüger's *Arch.*, vol. xii. p. 16: 1876. Compare Nencki, *Journ. f. prakt. Chem.*, vol. xxiii. p. 87: 1880; and Baumann, *Zeitschr. f. physiol. Chem.*, vol. v. p. 244: 1881.

[3] Compare Br. Radziszewski, "Zur Theorie der Phosphorescenzerscheinung," *Ber. d. deutsch. Chem. Ges.*, vol. xvi. p. 597: 1883.

access of atmospheric oxygen to the internal parts of the stack, the whole blazes up and is consumed.[1]

The rapid oxidation of food-stuffs which takes place in our tissues offers no mystery if the analogies that we have dwelt upon are taken into consideration. We must however not forget that the participation of active oxygen in the process is at present only an hypothesis, and that the facts are capable of another explanation.

The following facts observed by me[2] are not explicable on Hoppe-Seyler's hypothesis. Certain intestinal parasites, especially ascarides, can live and perform vigorous movements for several days without oxygen (compare Lecture XXIII.). The kinetic energy of these movements can only come from processes of disintegration, and we should therefore expect, according to Hoppe-Seyler, that hydrogen would be produced together with easily oxidizable substances. This is not the case. The animals give off a quantity of gas, which can be proved to consist of pure carbonic acid, since it is entirely absorbed by potash. No hydrogen was therefore formed. When I brought oxygen in contact with the fluid in which the worms had lived without oxygen for several days, and had during this time carried out active movements, no oxygen was absorbed. We must conclude therefore that no easily oxidizable products had arisen as a result of the disintegrative processes.

Another hypothesis, first started by Moritz Traube,[3] seems to me therefore worthy of attention. I refer to the idea that 'oxygen-carriers' are the active factors in the chemical processes of our body. By this term are meant substances which combine loosely with oxygen and readily give it up to others which do not directly unite with oxygen. A well-known example of such an oxygen transport is seen in the part played by nitric oxid in the preparation of sulphuric acid. Sulphurous acid cannot unite with oxygen directly. But if nitric oxid be present, sulphuric acid results; for the former body forms a loose compound with oxygen, and gives up the oxygen to the sulphurous acid. A small quantity of nitric oxid is capable of converting an unlimited quantity of sulphurous into sulphuric acid.

A similar action to that of nitric oxid in the oxidation of

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[1] This process so long known to farmers has recently been the subject of numerous chemical investigations. A summary of these experiments will be found in the *Chem. Centralbl.*, p. 316, year 17: 1886. Compare also Th. Schlösing, *Compt. rend.*, vol. cvi. p. 1293: 1888, and vol. cviii. p. 527: 1889.

[2] G. Bunge, *Zeitschr. f. physiol. Chem.*, vol. xiv. p. 318: 1890.

[3] M. Traube, "Theorie der Fermentwirkungen": Berlin, 1858.

sulphurous acid is manifested by sulphindigotate of potassium in the oxidation of grape-sugar. If a solution of grape-sugar be heated in the presence of air with some carbonate of soda, only a very insignificant and unimportant absorption of oxygen takes place. But if sulphindigotate of potassium be present, it gives up its loosely combined atom of oxygen to the grape-sugar and becomes decolorized. On shaking up the solution with air it again becomes blue; the sulphindigotate of potassium has again taken up oxygen from the air. On letting the solution stand for a brief period it again becomes decolorized. The blue color remains permanent only at the surface, where the solution continues in constant contact with the air. In this manner a small quantity of sulphindigotate of potassium is able to effect the oxidation of large quantities of grape-sugar, provided a free admission of atmospheric air be allowed.

The same result can also be produced by cupric oxid. A blue ammoniacal solution of cupric oxid is decolorized when heated with grape-sugar. The cupric oxid is reduced to cuprous oxid; it has given up one atom of oxygen to the grape-sugar. On shaking it up with air it again becomes blue, and so on. The cuprous oxid here plays the same part as oxygen-carrier that the nitric oxid does in the formation of sulphuric acid.

The oxidation of oxalic acid in the presence of a salt of iron affords another example. Under the influence of light, oxalic acid is oxidized, carbonic acid is formed, while the ferric oxid is reduced; the admission of air causes the ferrous oxid thus formed again to absorb oxygen; and thus a small amount of ferric salt has the power of gradually causing the oxidation of a large quantity of oxalic acid.[1] A similar part may possibly be played by the iron in our tissues, since this substance is present in loose combination wherever proteid and nuclein are to be found.

A familiar example of this carriage of oxygen is to be seen in the oxidation by means of atmospheric oxygen of methyl and ethyl alcohol vapors to formic and acetic acids, in the presence of finely divided platinum, *e. g.*, spongy platinum. Here also we might consider the metal as an oxygen carrier, though chemists are generally content to speak more vaguely of a 'contact effect.' Many attempts have been made to show that in this process the platinum could be replaced by organic substances, by 'ferments.' It is still undecided however whether organized ferments may not have been responsible for all these fermentative processes, as *e. g.*, the mycoderma aceti in

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[1] Pfeffer, *Unters. aus dem botan. Institut zu Tübingen*, vol. i. p. 679: 1885.

the rapid process of vinegar-making. We cannot however exclude the possibility that unorganized ferments may also effect the oxidation. We have already seen how the same result may be produced by a metal, an organic substance or a living cell. In the same way ferments might be the oxygen carriers in our tissues. They must however be much more energetic in their action than the mycoderma aceti, since alcohol is oxidized in our body to its end-products, carbonic acid and water, and does not stop at the stage of acetic acid. We should have to assume the presence in our tissues of ferments which, in the shortest possible time, converted fats, carbohydrates, and proteids into their end-products, carbonic acid, water, urea, and sulphuric acid.

The theory of the presence of active oxygen in the tissues has also been shown to be at variance with the fact that certain very readily oxidizable substances remain wholly or partially unaltered in their passage through the tissues of our body, such as pyrogallol,[1] pyrocatechin,[2] and phosphorus.[3] Carbonic oxid[4] which is converted into carbonic acid by nascent oxygen, and oxalic acid which is so readily oxidizable,[5] are quite unaltered in the organism.

But these facts too may be explained in another way. Every molecule, while on its travels, does not necessarily reach that point where it would meet with nascent oxygen. It even appears a plausible assumption that substances which do not belong to normal nutrition, or such as are poisonous, do not reach those cells in which the most intense oxidation occurs, to constitute a source of energy for the performance of normal functions. These cells, like all others, make their choice; they work with definite material, and reject that which is likely to be injurious.

Another explanation of the fact that pyrogallol and pyrocatechin do not become oxidized, is that they do not circulate in a free state through the body, but, like all hydroxyl derivatives of the aromatic hydrocarbons, *i. e.*, all phenols, com-

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[1] Cl. Bernard, "Leçons sur les propriétés physiologiques, &c., des liquides de l'organisme," vol. ii. p. 144: 1859; Baumann and Herter, *Zeitschr. f. physiol. Chem.*, vol. i. p. 249: 1877.

[2] Baumann and Herter, *ibid.*, p. 249.

[3] Hans Meyer, *Arch. f. exper. Path. u. Pharm.*, vol. xiv. p. 329: 1881. The previous literature on this subject will be found quoted here.

[4] Gaetano Gaglio, *ibid.*, vol. xxii. p. 236: 1887. In Gaglio's experiments the carbonic oxid was inspired. St. Zaleski (*ibid.*, vol. xx. p. 34: 1885) found that, after intraperitoneal injection of carbonic oxid blood, no carbonic oxid was given out by the lungs. It thus appears that carbonic oxid, introduced in this way, becomes oxidized.

[5] Gaglio, *loc. cit.*, p. 246.

bine with the sulphuric acid which arises from the decomposition of the proteids in the tissues. The phenols play the same part here that the alcohols do in the formation of the sulphuric ethers. A union accompanied by dehydration takes place; the sulphuric acid is converted from a dibasic into a monobasic acid, and reappears in the urine as an alkaline salt.

These conjugated sulphuric acids were discovered by Baumann. He showed that the urine of herbivora always contains an abundance of phenolsulphate of potassium.[1] Together with this another conjugated sulphuric acid occurs, in which the phenol is replaced by a methylated phenol called cresol,[2] and also sulphuric acid conjugated with pyrocatechin[3] and with indoxyl.[4] These combinations were also found to be invariably present in human urine, and only absent in the urine of carnivora if nothing but meat were eaten. If however phenol be administered to dogs, it appears in the urine as the corresponding conjugated sulphate (compare Lectures XXI. and XXII.).

It seems that sulphuric acid which, being the extreme stage of oxidation of sulphur, is not capable of further oxidation, also protects the organic conjugate against oxidation, even if the latter belongs to the group of fats. Salkowski[5] found that ethylsulphuric acid, when given to a dog, passed unaltered into the urine.

The question whether the nucleus of benzol is ever broken up by the decomposing and oxidizing agents occurring in our tissues, has not yet been settled. All aromatic compounds, whose behavior in the animal body has been examined in detail, reappear in the urine as aromatic compounds, although mostly in an altered form. Thus it is certain that benzoic and salicylic acids, when introduced into the body, can be entirely recovered from the urine, either unaltered or combined with glycin to form hippuric acid or salicyluric acid respectively.[6] (Compare Lecture XIX.) But the experiments with other aromatic compounds have not been executed quantitatively. The possibility remains that at least a small part is decomposed. Outside the organism, benzol can be oxidized by the action of ozone at an ordinary temperature, and thus converted into carbonic acid, oxalic acid, formic acid, acetic acid, and an

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[1] Baumann, Pflüger's *Arch.*, vol. xii. p. 69: 1876; and vol. xiii. p. 285: 1876.

[2] C. Preusse, *Zeitschr. f. physiol. Chem.*, vol. ii. p. 355: 1878; and Brieger, *ibid.*, vol. iv. p. 204: 1880.

[3] Baumann, Pflüger's *Arch.*, vol. xii. p. 63: 1876.

[4] Baumann and L. Brieger, *Zeitschr. f. physiol. Chem.*, vol. iii. p. 254: 1879.

[5] E. Salkowski, Pflüger's *Arch.*, vol. xii. p. 63: 1876.

[6] W. v. Schröder, *Zeitschr. f. physiol. Chem.*, vol. iii. p. 327: 1879; U. Mosso, *Arch. f. exper. Path. u. Pharm.*, vol. xxvi. p. 267: 1889.

amorphous black residue.[1] Should a really active oxygen be demonstrated as existing in our tissues, we might infer that a complete decomposition of the benzol would also occur in them.

Phenol is oxidized and split up by permanganate of potassium in an alkaline solution, with the production of oxalic acid. This fact led Salkowski [2] to examine the blood of rabbits poisoned by phenol for oxalic acid. Oxalic acid was detected in two out of three cases, but not in the blood of two healthy rabbits.

Experiments carried out by Tauber [3] and Auerbach [4] in Salkowski's laboratory and by Schaffer [5] in Nencki's laboratory, showed equally that if phenol be given to dogs, only a part, varying from 30 to 70 per cent. according to the amount introduced, ever reappears in the urine and feces. But it should not be immediately assumed that the phenol which has disappeared, has undergone combustion. It is quite possible that the benzol was not destroyed, but that the phenol had passed into another aromatic compound. Schaffer in fact found, in two experiments in which he estimated the amount of conjugated sulphuric acids, that these latter were increased after the addition of phenol, and in the exact ratio of the amount of phenol administered. No increase of oxalic acid in the urine could be detected in these experiments, nor in those of Tauber and Auerbach. Nor was the latter able to find any oxalic acid in the blood.

After Schotten [6] and Baumann [7] had introduced certain aromatic amido-acids, with three carbon atoms in the side-chain (tyrosin, phenylamidopropionic and amidocinnamic acids), into the organism of men, dogs, and rabbits, they could find no increase of any known aromatic compound in the urine. Hence they concluded that these aromatic compounds had been completely oxidized.[8]

Finally N. Juvalta [9] has shown by careful quantitative experiments that phthalic acid is in great part destroyed in the

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[1] Leeds, *Ber. d. deutsch. chem. Ges.*, vol. xiv. p. 975 : 1881.

[2] Salkowski, Pflüger's *Arch.*, vol. v. p. 357 : 1872.

[3] Tauber, *Zeitschr. f. physiol. Chem.*, vol. ii. p. 366 : 1878.

[4] Auerbach, Virchow's *Arch.*, vol. lxxvii. p. 226 : 1879.

[5] Schaffer, *Journ. f. prakt. Chem.*, N. F., vol. xviii. p. 282 : 1878.

[6] Schotten, *Zeitschr. f. physiol. Chem.*, vol. vii. p. 23 : 1882; and vol. viii. p. 60 : 1883.

[7] Baumann, *ibid.*, vol. x. p. 130 : 1886. Compare also K. Baas, *ibid.*, vol. xi. p. 485 : 1887.

[8] *Vide* also Nencki and P. Giacosa, *ibid.*, vol. iv. p. 328 : 1880.

[9] N. Juvalta (Bunge's laboratory), *Zeitschr. f. physiol. Chem.*, vol. xiii. p. 26 : 1888.

organism of dogs. Of 22.4 grms. which had been introduced into the stomach, only 7 grms. reappeared in the urine and feces. No other aromatic compounds were to be found.

What is actually known concerning the changes which aromatic compounds undergo through oxidation in the animal body is as follows:

The hydrocarbons are hydroxylized, the benzol being converted into oxybenzol and dioxybenzol[1]—hydrochinon and pyrocatechin. Oxidation does not advance a step further; for, after the administration of a few milligrammes of dioxybenzol (pyrocatechin), it reappears unaltered in the urine.[2]

If the aromatic combination introduced into the animal body has a side-chain belonging to the fat-group, it is in most cases attacked by oxygen.[3] Thus toluol ($C_6H_5-CH_3$), ethylbenzol ($C_6H_5-C_2H_5$), propylbenzol ($C_6H_5-C_3H_7$), benzylalcohol ($C_6H_5-CH_2OH$), are all converted by oxidation into benzoic acid (C_6H_5COOH). On the contrary, phenylacetic acid ($C_6H_5-CH_2-COOH$) is not attacked by oxygen. The inoxidizable carboxyl group appears in this case to protect the adjoining carbon atom in the same way as we have seen happen in the inoxidizable sulphuric acid. Group CH_2 in phenylacetic acid is protected on one side by the indestructible benzol ring, on the other by carboxyl. But if more than one atom of carbon is inserted between the benzol ring and carboxyl, this protection does not suffice. Phenylpropionic acid ($C_6H_5-CH_2-CH_2-COOH$) and cinnamic acid ($C_6H_5-CH{=}CH-COOH$) are converted into benzoic acid (C_6H_5COOH) by oxidation. If more than one side-chain be present of the benzol nucleus, only one of them is converted by oxidation into carboxyl. Thus the following changes are produced by oxidation:—

$$\begin{array}{llll}
\text{Xylol, } C_6H_4\left\{\begin{matrix} CH_3 \\ CH_3 \end{matrix}\right\} & \text{is converted into} & C_6H_4\left\{\begin{matrix} CH_3 \\ COOH \end{matrix}\right\} & \text{toluylic acid.} \\
\text{Mesitylene, } C_6H_3\left\{\begin{matrix} CH_3 \\ CH_3 \\ CH_3 \end{matrix}\right\} & \text{“} \quad \text{“} & C_6H_3\left\{\begin{matrix} CH_3 \\ CH_3 \\ COOH \end{matrix}\right\} & \text{mesitylenic acid.} \\
\text{Cymol, } C_6H_4\left\{\begin{matrix} C_3H_7 \\ CH_3 \end{matrix}\right\} & \text{“} \quad \text{“} & C_6H_4\left\{\begin{matrix} C_3H_7 \\ COOH \end{matrix}\right\} & \text{cuminic acid.}
\end{array}$$

In the animal body many aromatic compounds enter into combination with members of the fat-group which are easily oxidizable, and protect these from oxidation. The best-known

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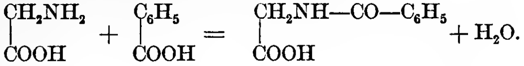
[1] Baumann und C. Preusse, *Zeitschr. f. physiol. Chem.*, vol. iii. p. 156: 1879.

[2] De Jonge, *ibid.*, vol. iii. p. 184: 1879.

[3] Schultzen und Naunyn, Reichert and Du Bois' *Arch.*, p. 349: 1867; Nencki and P. Giacosa, *Zeitschr. f. physiol. Chem.*, vol. iv. p. 325: 1880.

instance of this kind is the formation of hippuric acid from glycocol and benzoic acid—



$$\begin{array}{l}CH_2NH_2\\ |\\ COOH\end{array} + \begin{array}{l}C_6H_5\\ |\\ COOH\end{array} = \begin{array}{l}CH_2NH\text{—}CO\text{—}C_6H_5\\ |\\ COOH\end{array} + H_2O.$$

When no aromatic compounds are present in the animal body, glycocol undergoes complete oxidation, and is converted into carbonic acid, water, and urea (see Lecture XIX.); but, by uniting with the indestructible benzoic acid, it is protected against the influence of oxygen, and appears in the urine as hippuric acid (see Lecture XIX.).

Schmiedeberg and his pupils[1] have observed an interesting synthetic process of this kind in which a product of the oxidation of sugar unites with an aromatic compound, and is thus protected against further decomposition and oxidation. If camphor ($C_{10}H_{16}O$) be administered to a dog, this substance is hydroxylized in the same way as we have seen happen with regard to benzol; and campherol [$C_{10}H_{15}(OH)O$] is formed. But this product does not pass as such into the urine, but combined with glycuronic acid, with which it has united with dehydration. The formula of glycuronic acid is $C_6H_{10}O_7$ and, judging from all its properties and reactions, it must be regarded as a derivative of grape-sugar, and as a result of incipient oxidation.[2] If we break up the compound of campherol and glycuronic acid by boiling with dilute acids, the liberated glycuronic acid is rapidly decomposed; it becomes brown, and carbonic acid is developed. It is difficult to obtain a satisfactory quantity undecomposed for analysis. The ease with which this acid is decomposed and oxidized explains why we do not meet with it in the normal metabolism of animals. Here we find that the sugar, as soon as its oxidation has commenced, is rapidly decomposed into carbonic acid and water. It appears that fats offer definite points of attack for oxygen; and if these points are protected by non-oxidizable substances, the oxygen is unable to operate upon them. As soon as these points are undefended, they are rapidly decomposed and oxidized.

Schmiedeberg[3] has met with glycuronic acid a second time under different circumstances. He fed a dog on food containing no proteid, such as bacon and starch paste, and then

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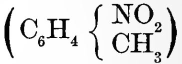
[1] C. Wiedemann, *Arch. f. exper. Path. u. Pharm.*, vol. vi. p. 230 : 1877; Schmiedeberg and Hans Meyer, *Zeitschr. f. physiol. Chem.*, vol. iii. p. 422 : 1879.

[2] On the chemical properties of glycuronic acid, *vide* H. Thierfelder, *ibid.*, vol. xi. p. 388 : 1887.

[3] Schmiedeberg, *Arch. f. exper. Path. u. Pharm.*, vol. xiv. pp. 306, 307 : 1881.

administered benzol. In order to form phenolsulphuric acid, the organism in this case had at its disposal only a minute quantity of sulphuric acid, resulting from the decomposition of proteids in the tissues—no sulphur having been introduced with the food. It follows that all the phenol formed from the benzol did not appear in the urine conjugated with sulphuric acid. It was proved that a part appeared as conjugated glycuronic acid.

Other inquirers have also repeatedly met with glycuronic acid. Jaffé[1] found that orthonitroluol  $\left(C_6H_4\left\{\begin{matrix}NO_2\\CH_3\end{matrix}\right.\right)$ is converted, in the dog, into orthonitrobenzyl alcohol  $\left(C_6H_4\left\{\begin{matrix}NO_2\\CH_2OH\end{matrix}\right.\right)$. This alcohol appears in the urine conjugated with an acid, which seems to be identical with Schmiedeberg's glycuronic acid. Mering and Musculus[2] found, in the urine of men and dogs to whom hydrate of chloral or of butylchloral had been administered, the corresponding alcohols, trichlorethylalcohol and trichlorbutylalcohol conjugated with glycuronic acid. It is to be noted that in this process the conjugate of glycuronic acid is formed by reduction, while in the processes observed by Schmiedeberg and Jaffé, it was due to oxidation. Again, in the experiments of Mering and Musculus, it was not an aromatic compound which protected the glycuronic acid from oxidation, but one belonging to the fatty series, which had been rendered more or less incombustible by chlorin.

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[1] Jaffé, *Zeitschr. f. physiol. Chem.*, vol. ii. p. 47 : 1878.

[2] Von Mering and Musculus, *Ber. d. deutsch. chem. Ges.*, vol. viii. p. 662 : 1875 ; von Mering, *Zeitschr. f. physiol. Chem.*, vol. vi. p. 480 : 1882. *Vide* also Külz, Pflüger's *Arch.*, vol. xxviii. p. 506 : 1882 ; and Kossel, *Zeitschr. f. physiol. Chem.*, vol. iv. p. 296 : 1880 ; and M. Lesnik, *Arch. f. exper. Path. u. Pharm.*, vol. xxi. p. 168 : 1887.

LECTURE XVIII

THE GASES OF THE BLOOD AND RESPIRATION (*continued*)—BEHAVIOR OF CARBONIC ACID IN THE PROCESSES OF INTERNAL AND EXTERNAL RESPIRATION—CUTANEOUS RESPIRATION—INTESTINAL GASES

In our previous remarks on the gases of the blood and on respiration we have become acquainted with the behavior of oxygen and the processes of oxidation in the tissues. It now only remains for us to consider the ultimate gaseous product of the processes of oxidation and decomposition, CARBONIC ACID, together with its behavior in the processes of internal and external respiration.

In the venous blood of the dog, the carbonic acid amounts to from 39 to 48 vols. per cent. (reckoned at 0° C. and 760 mm. Hg.); in the arterial, to an average of about 8 vols. per cent. less.[1]

Carbonic acid, like oxygen, is not simply absorbed in the blood, as there is far too large an amount. Water absorbs double its own bulk from an atmosphere of pure carbonic acid, at 0° C.; at the temperature of a room, it absorbs its own volume, and at the temperature of the body, half its volume or 50 vols. per cent. of this gas. Very nearly as much as this is contained in venous blood. If therefore the carbonic acid were simply absorbed, its partial pressure would amount to a whole atmosphere. This cannot be the case, for the partial pressures of all the gases of the blood together can never amount to much over an atmosphere.

The partial pressure of the carbonic acid in the blood is accurately known from the researches of Pflüger and his pupils Wolffberg,[2] Strassburg,[3] and Nussbaum.[4] They introduced blood from the vessels of a living dog into the upper end of a

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[1] A. Schöffer, *Wien. akad. Sitzungsber.*, vol. xli. p. 589 : 1860; Sczelkow, *ibid.*, vol. xlv. p. 171 : 1862.

[2] Wolffberg, Pflüger's *Arch.*, vol. iv. p. 465 : 1871; and vol. vi. p. 23 : 1872.

[3] Strassburg, *ibid.*, vol. vi. p. 65 : 1872.

[4] Nussbaum, *ibid.*, vol. vii. p. 296 : 1873.

vertical glass tube which contained nitrogen with a small percentage of carbonic acid. The blood ran down against the sides of the tube without coagulating, and was at once removed when it reached the lower end by a particular arrangement which prevented any air getting to it.[1] If the tension of the carbonic acid in the blood is greater than in the gas inside the tube, then the amount of carbonic acid in the gas must increase; if the tension in the blood is less, then the amount of carbonic acid in the gas must diminish. It was proved by numerous experiments that the pressure of CO_2 amounts to 54 per cent. of an atmosphere in the blood of the large veins of a dog and in that from the right heart, and to 2.8 per cent. in arterial blood.[2]

Now, as water at the temperature of the body takes up only about 50 vols. per cent. of CO_2 from an atmosphere of pure carbonic acid, it follows that venous blood, which is under a carbonic acid pressure of only 5 per cent. or $\frac{1}{20}$ of an atmosphere, cannot contain more than about $\frac{50}{20} = 2\frac{1}{2}$ vols. per cent. of CO_2 simply absorbed. The remaining 36 to 46 vols. per cent. must be in a state of chemical combination, and a glance at the composition of the ash of blood shows us that the substances, which fix carbonic acid, must be soda and potash. The ash of the plasma has never been analyzed. I found that serum, the ash of which cannot be of very different constitution from that of the plasma, has the following composition:—[3]

ONE THOUSAND GRAMMES OF SERUM FROM DOG'S BLOOD CONTAINS—

K_2O	0.202	Fe_2O_3	0.010
Na_2O	4.341	P_2O_5	0.489
CaO	0.176	Cl	3.961
MgO	0.041		

We need take no notice of the minute proportion of potassium, which probably arises mostly from the breaking up of the leucocytes, and of which there is only a trace in the plasma of the living blood. Nor is it necessary to take into consideration the small amount of lime and magnesia; they are for the most part combined with the albumins and nucleo-albumins, and perhaps are not at all concerned in fixing carbonic acid. Anyhow, the bulk of the carbonic acid in the plasma is com-

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[1] Diagrams and description of the apparatus are given by Strassburg, Pflüger's *Arch.*, vol. vi. p. 69: 1872.

[2] Strassburg, *loc. cit.*

[3] The analysis has been published only in part (*Zeitschr. f. Biolog.*, vol. xii. p. 204: 1876).

bined with sodium: 3.463 of the 4.341 grms. of sodium are sufficient to saturate the only strong mineral acid of the plasma, the hydrochloric acid. The remainder, 0.878 grm. of sodium, is able to fix 0.623 grm. CO_2 = 316 c.cms. carbonic acid gas (computed at 0° C. and 760 mm. Hg. pressure), besides an equal additional amount when the bicarbonate of soda is formed. 632 c.cms. of carbonic acid (*i. e.*, 63 vols. per cent.) may therefore be chemically combined in a liter of blood-plasma. It must however be remembered that the carbonic acid never really reaches quite 63 volumes per cent., as the 0.878 grm. sodium must be divided amongst the other weak acids—such as phosphoric acid, proteid, and perhaps many others, each of which is of little importance singly, but which altogether exert some influence. As a fact, from 43 to 57 vols. per cent. of carbonic acid have been found in arterial blood-serum of the dog. The amount of CO_2 must be still larger in the serum of venous blood, where the disposable sodium is perhaps almost completely saturated with carbonic acid. How large a share of the sodium falls to the lot of the carbonic acid depends on 'mass influence,' *i. e.*, on the partial pressure of the carbonic acid.[1] In the tissues where CO_2 is liberated by oxidation and decomposition, and its partial pressure rises, sodium bicarbonate must be formed at the cost of the sodium albuminate and of the dibasic sodium phosphate (Na_2HPO_4), which latter gives up one-half of its sodium and is converted into the acid salt (NaH_2PO_4). In the alveoli of the lungs, where the partial pressure of the carbonic acid is diminished in consequence of the constant mechanical ventilation, the blood gives off a portion of its carbonic acid by diffusion; the mass-influence of the CO_2 in the blood becomes lessened, and that of the other acids relatively increased; again sodium albuminate and dibasic sodium phosphate (Na_2HPO_4) are formed at the cost of the sodium bicarbonate. As soon as the amount of free carbonic acid decreases, however little, the amount of the loosely combined CO_2 also diminishes, and even to a considerable extent. By this arrangement the amount of carbonic acid of the blood can vary within wide limits without the total pressure of the gas being materially altered. A change of pressure up to 2.6 per cent. of an atmosphere produces an alteration of 8 vols. per cent. in the carbonic acid of the blood. This allows of large quantities of CO_2 being transported in a short time from the tissues into the lungs.

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[1] N. Zuntz, *Centralbl. f. d. med. Wissensch.*, p. 527 : 1867; F. C. Donders, Pflüger's *Arch.*, vol. v. p. 20 : 1872. *Vide* also J. Gaule, Du Bois' *Arch.*, p. 469 : 1878.

Hoppe-Seyler and his pupil Sertoli[1] have shown that proteid does indeed compete with the carbonic acid for the possession of the sodium. Proteid drives out carbonic acid in a vacuum from a solution of simple sodium carbonate; the amount driven out is however very small, as might *à priori* be anticipated, owing to the great molecular weight of the proteid.[2]

The occurrence of phosphates of the alkalies in the plasma has frequently been doubted.[3] The phosphoric acid in the ash has been ascribed to the lecithin and nuclein, but the amount is too large for this purpose, at any rate in dog's blood; in bullock's and pig's blood it is certainly much smaller.[4] But, at any rate, it is only a small portion of the alkalies which is combined with phosphoric acid in the plasma. In the corpuscles, on the contrary, there is no doubt that phosphates play an important part in fixing carbonic acid.

The way in which the phosphoric acid is driven from the possession of the sodium by the carbonic acid, and *vice versâ*, may be demonstrated by a simple experiment. If to a solution of Na_2HPO a few drops of litmus solution be added, the solution becomes blue. If CO_2 be now introduced the solution becomes red; the carbonic acid is not the cause of this change in color, as a control experiment shows, but the formation of NaH_2PO_4. $NaHCO_3$ is formed simultaneously. If the vessel be left open, the carbonic acid gradually disappears, the mass influence of the phosphoric acid becomes relatively greater, it again takes possession of the second sodium equivalent, of which it had been robbed by the CO_2, and the blue color reappears. This process can be hastened by boiling.

Carbonic acid is found not only in the blood-plasma but also in the corpuscles, though not in such large quantities. This follows from the simple fact that the total blood contains less CO_2 than the serum. But the difference is not sufficient to enable us to ascribe all the carbonic acid to the serum.[5]

The carbonic acid cannot be completely removed from the serum by the air-pump, a proof that the amount of the non-volatile weak acids is less than the equivalent of the 0.9 per 1000 sodium just estimated. But more than half can be removed,[6] a proof that the process is not merely a transition

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[1] Sertoli, Hoppe-Seyler's *Med. chem. Unters.*, Heft iii. p. 350: Berlin, 1868.

[2] Hoppe-Seyler, "Physiologische Chemie," p. 503: Berlin, 1879.

[3] Sertoli, *loc. cit.*

[4] *Vide* Bunge, *Zeitschr. f. Biolog.*, vol. xii. pp. 206, 207: 1876; and Sertoli, *loc. cit.*

[5] Alexander Schmidt, *Berichte über die Verhandlungen der königl. sächs. Ges. d. Wissensch. zu Leipzig*, Math. phys. Classe, vol. xix. p. 30: 1867.

[6] Pflüger, "Ueber die Kohlensäure des Blutes," p. 11: Bonn, 1864.

from sodium bicarbonate into carbonate, but also a partial displacement of the firmly combined carbonic acid by the other weak acids, proteid, phosphoric acid, &c.

The carbonic acid may, on the contrary, be completely pumped out of the blood.[1] And moreover Pflüger[2] has shown that if sodium carbonate be added to the blood, the CO_2 may be driven out even from this in a vacuum. In order to explain these facts, we must assume either that acids from the corpuscles diffuse into the plasma, or that sodium carbonate diffuses from the plasma into the corpuscles.

With regard to the acids of the blood-corpuscles, the most important place is held by the phosphoric acid, in which the corpuscles at any rate are far richer than the plasma. Only a very small portion of this large amount of phosphoric acid can be contained in the corpuscles as an organic compound. In the second place, probably the oxyhemoglobin is of influence for, as Preyer[3] has shown, it drives out CO_2 from sodium carbonate in a vacuum.

It has been much disputed whether the giving off of carbonic acid from the capillaries of the lungs into the air of the alveoli simply follows the laws of diffusion, or whether we must assume that special excretory forces are at work in the lung-tissue. The results of the following experiment of Pflüger and his pupils, Wolffberg[4] and Nussbaum,[5] are in favor of the former view. If the giving off of carbonic acid in the alveoli of the lungs simply follows the laws of the diffusion of gases, we should expect *à priori* that, if a lobe of the lung were blocked by closing the corresponding bronchus, the carbonic acid pressure would rise in the air-cavities of the lung thus closed in, until it balanced the carbonic pressure in the venous blood flowing in, and that then the blood flowing out, *i. e.*, the arterial blood of the pulmonary veins in this same lobe, would also have the same CO_2 tension. The experiments of Wolffberg and Nussbaum have in fact shown that, under these conditions, the pressure of CO_2 in the alveoli is the same as in the venous blood.

One pulmonary lobe was successfully closed in the following manner. An elastic catheter[6] was introduced into a branch of one bronchus of a dog that had been tracheotomized.

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[1] Setschenow, *Sitzungsber. d. Wien. Akad.*, vol. xxxvi. p. 293 : 1859.

[2] Pflüger, *loc. cit.*, pp. 5, *et seq.*

[3] W. Preyer, "Die Blutkrystalle" : Jena, 1871.

[4] Wolffberg, Pflüger's *Arch.*, vol. iv. p. 465 : 1871; and vol. vi. p. 23 : 1872.

[5] Nussbaum, *ibid.*, vol. vii. p. 296 : 1873.

[6] A description and illustration of the 'lung-catheter' are given by Wolffberg, *ibid.*, vol. iv. p. 467, &c. : 1871.

The catheter had a double wall; the outer, which was made of india-rubber, was thinner towards the end inserted in the bronchus, so that, when inflated, this end expanded, whilst the thicker portion of the wall remained the same. This flask-like expansion of the tube ensured a completely air-tight closure of the bronchus. Ventilation went on unimpeded in the other lobes of the same lung and in the other lung, so that there could be no retention of CO_2 in the blood. The pressure of carbonic acid was thus also normal in the blood-vessels of the lobe that had been stopped up. When the closure had lasted long enough, a sample of the gas could be drawn out through the inner tube of the catheter, and used for analysis. The means of numerous estimates of the enclosed pulmonary air gave an average pressure of CO_2 of 3.84 per cent. of an atmosphere, and of 3.81 per cent. for the blood from the right heart. The fact that the latter figure is lower than in the above-mentioned experiments of Strassburg, who found a mean of 5.4 per cent., is explained by the fact that the animals were not tracheotomized in Strassburg's cases, and that, in consequence of tracheotomy, the ventilation of the lung is far more complete, and the retention of carbonic acid in the blood is much less.

Under normal conditions, if the interchange of gas simply follows the laws of diffusion, the pressure of CO_2 could never be higher in the alveoli of the lungs than in the arterial blood, the two being equally balanced. If the balance is complete, the pressure must be the same; if incomplete, the pressure in the alveoli must be lower, but can never be higher. If it were, we should have to assume that forces were at work in the lung-tissue to expel it. How do the facts agree with this deduction? Strassburg found that the pressure of carbonic acid in the arterial blood of the dog was from 2.2 to 3.8 per cent., or on an average 2.8 per cent. of an atmosphere.[1]

The normal CO_2 pressure in the alveoli cannot be ascertained, but we can determine its minimal value by estimating the CO_2 pressure in the total air expired, which is a mixture of alveolar air and atmospheric air. If this minimal value should prove higher than the carbonic acid pressure in the arterial blood, the assumption that the interchange of gases proceeds only by diffusion would be refuted; we should be forced to consider that there were other special expelling forces at work.

The amount of carbonic acid in the expired air of the dog has, so far as I am aware, only been estimated once.

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[1] Strassburg, Pflüger's *Arch.*, vol. vi. p. 77: 1872.

Wolffberg[1] found from 2.4 to 3.4, a mean of 2.8 per cent. Wolffberg's dog was tracheotomized. The CO_2 tension in the expired air would be higher in a dog breathing normally, and still higher in the alveolar air than in the expired air. These experiments urgently require repetition. These facts, so far, are only partially reconcilable with the theory that the interchange of gases in the lungs proceeds merely according to the laws of diffusion.

The amount of CO_2 in the air expired by human beings is much larger: Vierordt[2] found 4.6 per cent. CO_2 in the air normally expired, and 5.2 per cent. in that expired after a very deep inhalation. The pressure of carbonic acid in the arterial blood of human beings is not known.

In the short time during which the blood flows through the capillaries of the lungs, the equalization of the difference in tension is accomplished with a completeness which is surprising. This phenomenon is explained if the extent of the surface be considered over which the interchange takes place. According to an approximate valuation of the anatomist Huschke, the total inner surface of the human lungs amounts to 2000 square feet, and the whole of this vast surface is thickly interwoven with a network of capillaries.

The experiments made to estimate the pressure of carbonic acid in the tissues are attended with great difficulties. *À priori*, it must be assumed that the greatest pressure will be where the development of carbonic acid is most considerable: therefore probably in the cells, in the muscular fibers, in all the active elements—in fact, wherever most kinetic energy is liberated. Now the pressure of CO_2 cannot be directly estimated in the cells themselves; an endeavor has therefore been made to estimate the partial pressure of this gas in the fluids which come most in contact with the cells, *i. e.*, the lymph. It was imagined *à priori* that the lymph, which flows so slowly round the cells, would be saturated far more completely with carbonic acid than the blood, which passes through the capillaries so rapidly. But as a matter of fact this is not so. Strassburg[3] found the tension of carbonic acid invariably less in the lymph than in venous blood. It thus appears that the stream of CO_2 from the cells into the lymph does not simply follow the laws of diffusion. Why does the bulk of it diffuse directly into the blood? The purpose is evident; the

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[1] Wolffberg, Pflüger's *Arch.*, vol. vi. p. 478 : 1871.

[2] Vierordt, "Physiol. des Athmens," p. 134 : Heidelberg, 1845.

[3] Strassburg, *loc. cit.*, pp. 85–91. *Vide* also Gaule, Du Bois' *Arch.*, pp. 474–476 : 1878.

carbonic acid reaches the lungs most rapidly in this manner. The cause, however, is not yet known.

Strassburg has also estimated the tension of carbonic acid in dog's urine, and found it to be about 9 per cent. of an atmosphere, and in the bile 7 per cent. Finally, he endeavored to estimate it in the tissues of the intestinal wall, by injecting atmospheric air into a ligatured coil of intestine of a living dog, and analyzing a sample of the air after from half an hour to three hours; he found from 7 to 9½ per cent. CO_2. From these facts it follows that the tension of carbonic acid is greater in the tissues than in the blood, which we should expect to be the case.

But what would happen if an animal were brought into an atmosphere where the pressure of carbonic acid was already as great as in the venous blood? The interchange of gases in the alveoli would be stopped, but only for an instant; for the development of carbonic acid proceeds unremittingly in the tissues. The amount of CO_2 rises above the normal both in the tissues and in the blood, and then it will again be given off by the walls of the alveoli, in consequence of the difference in tension which arises.

But a retention of carbonic acid in the blood and in the tissues will occur much sooner, long before the amount of CO_2 in the inspired air is the same as that of the normal alveolar air. The smaller the difference of the tension of carbonic acid in venous blood and in the alveolar air, the more slowly will CO_2 be given off from the blood to the alveolar air, and the greater must be the retention of carbonic acid in the blood and in the tissues.

The abnormally high tension of this gas in the tissues is the cause of disturbances, especially in certain parts of the central nervous system. The increasing partial pressure of the carbonic acid acts above all on the respiratory center, causing deeper respiration. If the retention of carbonic acid be so great that the deeper respiration cannot overcome it, it acts also on other parts of the central nervous system, and the animals finally die with symptoms of narcosis.

If animals be placed in an air-tight compartment, and be made to breathe an artificial mixture of air rich in oxygen, they die of carbonic acid poisoning long before the partial pressure of the oxygen has sunk to normal.[1]

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[1] Müller, *Sitzungsber. d. Akad. d. Wissensch. zu Wien.*, Math. Nat. Classe, vol. xxxiii. p. 136, *et seq.:* 1859; P. Bert, "La pression barométrique," p. 983: Paris, 1878; Friedländer and Herter, *Zeitschr. f. physiol. Chem.*, vol. ii. p. 99: 1878.

If the volumes of the inspired and expired air in normal respiration be compared, the latter is always found to be larger. The explanation is to be sought in the fact that the air has become warmer in the lung and, owing to the temperature of the body, has been almost saturated with aqueous vapor. The quantity of water which leaves the body in this way during the course of a day amounts to from 400 to 800 grms. It varies with the dryness of the inspired air.

But if, on the other hand, the volumes of the inspired and expired air be compared after desiccation, and reduced to the same temperature and pressure, the volume of expired air is usually somewhat smaller. This is readily explained if we consider that, in the combustion of food-stuffs, it is only the carbohydrates which produce a volume of carbonic acid equal to that of the oxygen used up, the proteids and fats yielding a smaller one.

The carbohydrates are known to contain exactly so much oxygen as is requisite for the saturation of the hydrogen. If therefore the entire molecule becomes oxidized to carbonic acid and water, exactly two oxygen atoms must be taken up to every carbon atom. Two atoms (that is, one molecule of oxygen) form with one atom of carbon one molecule of carbonic acid. Now, it is well known that an equal number of molecules occupies an equal volume. Consequently, the volumes of CO_2 formed during the combustion of the carbohydrates must be equal to the volume of oxygen used up.

The fats, on the other hand, contain fewer oxygen atoms than are necessary for the saturation of the hydrogen atoms: in stearic acids ($C_{18}H_{36}O_2$), only four of the thirty-six hydrogen atoms can be saturated by the oxygen present; sixteen more atoms of the inspired oxygen must be used up in order to complete the combustion of the hydrogen, and these do not reappear in the expired air. Glycerin ($C_3H_8O_3$) also contains two atoms more hydrogen than are saturated by the oxygen present. Thus, for the complete combustion of the fats, far more oxygen must be taken up than is requisite for the combustion of their carbon; and for this reason all the inspired oxygen does not reappear in the expired carbonic acid.

This is also the case with the proteids. One hundred grms. of proteid contain 7 grms. of hydrogen. In order to reduce these to water by combustion, $7 \times 8 = 56$ grms. of oxygen are necessary. But 100 grms. of proteid matter contain at most 24 grms. of oxygen. Extra oxygen must therefore be inspired for the purpose of oxidizing the hydrogen, besides the amount necessary for the oxidation of the carbon. Only the estimate is rendered more complicated with proteid, because hydrogen and oxygen atoms are also eliminated in the nitrogenous waste products, and because oxygen is also used up in oxidizing the sulphur.

The proportion of the expired volume of carbonic acid to the inspired volume of oxygen is termed the respiratory quotient.

The carbohydrates preponderate in the diet of herbivora. The respiratory quotient in these cases is nearly equal to 1. With carnivora, on the other hand, where the food is poor in carbohydrates and rich in proteids and fats, the respiratory quotient must be considerably less than 1. It is usually found to be about $\frac{3}{4}$.

The respiratory quotient estimated from the constituents of food only agrees with that actually found[1] if the estimation of the respiratory gases be carried out for some time, if possible for twenty-four hours. In short spaces of time, the proportion may be very materially altered, because the taking in of oxygen and the giving out of carbonic acid do not occur simultaneously. A considerable part of the carbon may be split off from the carbohydrates as carbonic acid without any oxygen being taken in, as we see in alcoholic and butyric acid fermentation; the by-products then formed, which are poor in oxygen, are oxidized later, after the CO_2 previously given off has been expired. In this way it may happen that the expired volume of CO_2 may for a time be larger than the inspired oxygen volume, and the respiratory quotient may be greater than 1.

In herbivora, it sometimes happens that the whole volume of CO_2 expired in twenty-four hours is larger than the volume of inspired oxygen. The following statement will explain this.

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[1] A description and illustration of the apparatus used for the quantitative estimate of the interchange of gases during longer periods, and especially of Regnault's, Reiset's, and Pettenkofer's respiratory apparatus, are to be found in every text-book of physiology. Any one desirous of reading the original description by the authors, is referred to the celebrated work of Regnault and Reiset in the *Ann. de Chim. et de Phys.*, vol. xxvi.: 1849; also under the separate title, "Recherches chimiques sur la respiration des animaux des diverses classes": Bachellier, 1849; translated in Liebig's *Ann. d. Chem. u. Pharm.*, vol. lxxiii. pp. 92, 129, 257: 1850. The description of Pettenkofer's respiratory apparatus is to be found in Liebig's *Ann. de Chem. u. Pharm.*, vol. ii. p. 1, Suppl.: 1862. This apparatus was specially constructed for experiments on human beings. Voit modified it somewhat for smaller animals. The exact illustration and description are given in *Zeitschr. f. Biolog.*, vol. xi. p. 541: 1875. A modification of Regnault's and Reiset's apparatus for examining the respiration of aquatic animals was described by Jolyet and Regnard in *Arch. de physiol. normale et patholog.*, sér. ii. vol. iv. p. 44: 1877. More recently Hoppe-Seyler has constructed a respiratory apparatus on Regnault's principle for experiments on man. *Zeitschr. f. physiol. Chem.*, vol. xix. p. 574: 1894.

Vegetable food contains organic acids, which are richer in oxygen than the carbohydrates, and for this reason they use up, during their conversion into carbonic acid and water, a smaller volume of oxygen than that corresponding to the volume of carbonic acid formed. Tartaric acid with 2½ vols. of oxygen gives 4 vols. of CO_2: $C_4H_6O_6 + 5O = 4CO_2 + 3H_2O$. But carbonic acid may be developed from another source without oxygen being taken up. The carbohydrates may undergo marsh-gas fermentation in the intestine: $C_6H_{12}O_6 = 3CO_2 + 3CH_4$. The carbonic acid is absorbed from the intestine and breathed out from the lungs, but the marsh-gas remains unoxidized (pp. 279, 280).

It is important to know all these conditions upon which the respiratory quotient depends. In the experiments on metabolism, the size of this quotient affords many indications from which the chemical processes in the tissues may be judged.

In speaking of respiration, we have hitherto meant only the respiration through the lungs. The question now remains for us to consider whether there is, in human beings, such a thing as CUTANEOUS RESPIRATION. It undoubtedly exists among the lower animals, as well as among certain of the lower vertebrata. Among the amphibia, the interchange of gases goes on more extensively by means of the skin than by the lungs. This was known even to Spallanzani.[1] He proved that many kinds of amphibia lived longer after extirpation of the lungs than after their skins were varnished over. There is however this objection to the above experiment, *i. e.*, that the varnishing of the skin would be prejudicial in other ways. Spallanzani's experiments have therefore been repeated with many alterations.[2] Fubini estimated the whole of the CO_2 given out by normal frogs and, on comparing it with that given out by frogs with their lungs extirpated, found that the latter amount was only a little less. To this experiment the objection may also be raised that after extirpation of the lungs the output of CO_2 by the skin was no longer normal, but increased by vicarious activity. Ferd. Klug therefore constructed a special apparatus, in which the head and body were each in separate compartments. The separation was effected by means of a sheet of india-rubber, through which the head was passed. The result

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[1] Spallanzani, "Mémoires sur la respiration, traduits par Senebier," p. 73 : Genève, 1803.

[2] *Vide* Fubini, Moleschott's *Unt. z. Naturlehre*, vol. xii. p. 100 : 1878 ; and Ferd. Klug, Du Bois' *Arch.*, p. 183 : 1884, containing also a critical notice of the earlier literature.

of this experiment was found to be that only a very small part of the CO_2 was given out through the lungs.

The most exact estimates on the output of CO_2 through the skin of human beings were made by H. Aubert.[1] The person experimented on sat naked in an air-tight box, the top of which was made of india-rubber. The head came out of a round hole in this covering, which fitted tightly round the neck, so that no air could get in. A stream of air was now admitted into the enclosed space. The air had been previously freed from all carbonic acid, and on coming out was passed through flasks containing baryta water. The experiment lasted for two hours. From the carbonic acid absorbed during this time by the solution of baryta, the quantity eliminated in twenty-four hours was estimated. Seven experiments showed that in twenty-four hours a man gives out by the skin a maximum of 6.3 grms., a minimum of 2.3, or an average of 3.9 grms. of carbonic acid.

This amount of CO_2 is exceedingly small in comparison with that proceeding from the lungs, which in human beings amounts to from 800 to 1200 grms. in twenty-four hours. It is even doubtful whether the small quantity of CO_2 found was really given off by the skin in the form of gas. It is possible that it arose from the decomposition of the secretions of the skin and of the cast-off epidermis. Still more dubious are the statements that small quantities of oxygen are taken up through the human skin.

Until quite recently, it was believed that not only is carbonic acid given out through the skin, but also certain gaseous organic compounds of a more complex nature. This has been the explanation offered for the injurious effects of a great many people being shut up together in a small room. It was thought that these organic vapors have a very low tension; that the air soon reaches saturation as far as they are concerned, and cannot receive any more of them from the organism, unless it be rapidly changed and renewed. If these vapors, in however small a quantity, remain behind and collect in the body, they act on certain parts of the nervous system, and through these on the whole metabolism, just as they do on our olfactory nerves after they have passed into the air, when they may even cause vomiting.[2]

This idea of the injurious effects arising from the suppressed action of the skin is as old as the history of medicine, and even up to the present time the *perspirabile retentum* plays an important part in the etiology of certain diseases. This idea in-

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[1] H. Aubert, Pflüger's *Arch.*, vol. vi. p. 539 : 1872.

[2] Pettenkofer, Liebig's *Ann. d. Chem. u. Pharm.*, vol. ii. Suppl. p. 5 : 1862.

duced Pettenkofer, in his researches on respiration, to abandon the method of Regnault and Reiset, and to construct a new respiratory apparatus, in which a constant current of fresh air passed through the compartment that held the person or animal. Pettenkofer had found that when the proportion of CO_2 had risen to 0.1 per cent. in a room filled with people, the air began to smell, and that when it rose to 1 per cent. the air became almost unendurable. But if he developed carbonic acid in a room, by acting on bicarbonate of sodium with sulphuric acid until the CO_2 in the air amounted to 1 per cent., he found that he could remain in this room quite comfortably for a considerable time. It is therefore not the carbonic acid itself that is the harmful product in so-called bad air; but, according to Pettenkofer, the CO_2 is a measure of the injurious products of perspiration which are as yet unknown to us.

All endeavors to discover what these harmful products of perspiration are have hitherto failed. The latest experiments were made by Hermans[1] in the Institute of Hygiene in Amsterdam. A man was shut in an air-tight case of sheet-iron. The first signs of dyspnea appeared when the CO_2 in the air rose above 3 per cent. If the carbonic acid was removed by absorption, no inconvenience was experienced, even when the amount of oxygen in the box sank to 10 per cent. In order to discover the supposed organic products of perspiration, air was first passed through the case, and then through an absorption apparatus. When passed through titrated sulphuric acid, the titre was always found to be unaltered. If the air was passed over red-hot oxid of copper, the amount of CO_2 and of water did not increase. In the same way the titre of a boiling acid or alkaline permanganate solution was found to be unchanged, even after many liters of the air taken from the case towards the end of the experiment had been slowly passed through it. Neither did the condensed water, obtained from the issuing air after being cooled by ice, nor the condensed water from the sides of the case, alter the titre of boiling permanganate solution. There was likewise no disagreeable smell. The greatest care had been taken to see that the clothing and person of the man experimented upon were perfectly clean. Hermans therefore comes to the conclusion that when healthy people give out malodorous substances in the atmosphere, these come, not from normal perspiration, but from the processes of decomposition caused by the dirty state of the body or clothes.

The medical men who believe in the harmfulness of the *perspirabile retentum*, ground their belief on the following facts:

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[1] Hermans, *Arch. f. Hygiene*, vol. i. p. 5: 1883.

(1) The injurious effect on animals whose skin has been rendered impervious to perspiration by varnishing; and (2) the fatal effect of extensive burns of the skin. But these facts must be differently interpreted.

The death of varnished animals may be explained by an increased loss of heat.[1] In the first place, the animals in all such experiments were shaved before being varnished, thus being deprived of their natural protection; in the second place, the varnishing appears to damage the vasomotor nerves; the cutaneous vessels become dilated, the surface of the body becomes warmer than it normally is, and the loss of heat is greater. In consequence of this, the temperature of the body sinks; and the animals die of cold. If an animal be only partially varnished, it is found that the varnished parts are warmer than the rest of the skin. A varnished animal gives out more heat in the calorimeter than a normal one does. If the cooling be prevented by wrapping the varnished animal in wool, or by placing it in a warm place, it remains alive and does not become ill. Besides, only those animals fall ill on being varnished that have a delicate skin, and a surface that is large in proportion to their small weight, as for instance rabbits. Larger animals with a tough skin, such as dogs, remain perfectly well with their whole body varnished over.

Senator,[2] in Berlin, even ventured to varnish human beings. He had two patients suffering from rheumatism, which is often thought to be caused by the arrest of the action of the skin. Any interference with this action should therefore be attended with dire consequences. The extremities of these patients were encased in sticking-plaster, and almost the whole trunk was thickly painted with collodion, mixed with a little castor oil to make it less brittle. Only the skin of the head, neck, buttock, and genitals remained free. One patient twice remained in this condition for twenty-four hours, the other for fully eight days! The third experiment was made on a female patient with chronic pemphigus. The whole body, and even the face, was thickly covered with common tar, and the head, which had been shaven, with oleum rusci.[3] This air-tight

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[1] Laschkewitsch, *Arch. f. Anat. u. Physiol.*, p. 61: 1868; R. Winternitz, *Arch. f. exper. Path. u. Pharm.*, vol. xxxiii. p. 286: 1894.

[2] Senator, Virchow's *Arch.*, vol. lxx. p. 182: 1877.

[3] [Oleum rusci sive pix betulimum sive oleum betulæ empyreumaticum, is a tarry product obtained from all parts of the birch tree, and in great favor as a popular remedy for all kinds of diseases in Poland and Russia. It is also employed in the fabrication of certain liqueurs, and especially in the preparation of Russian leather, to which it imparts its characteristic odor (see Dr. Hager's "Handbuch der pharmaceutischen Praxis": Berlin, 1880; and the *United States Dispensary:* 1883).]

covering was not removed for ten days, but no injurious consequences occurred in any of the three cases.

Finally, as regards the fatal effect of extensive burns on the skin, there may be other explanations than that of the *perspirabile retentum;* in fact, in recent times many others have been attempted. We know that even a moderate rise of temperature will alter and destroy the blood-corpuscles.[1] This led to the supposition that the blood-cells which pass through the capillaries of the skin during a burn become destroyed by the higher temperature, and that their decomposition-products indirectly cause the symptoms which ensue. And in fact a constituent of the corpuscles, the hemoglobin, was found in the plasma of the blood after a burn, and the hemoglobin, or a derivative, was found in the urine.[2] According to Hoppe-Seyler's[3] and Tappeiner's[4] investigations, however, the amount of hemoglobin in the blood-plasma after burns is very slight, and was even entirely absent in one case which ended fatally. Neither it nor its derivatives invariably occur in the urine. On the other hand, the following fact observed by Tappeiner is very interesting: he found the blood of patients with extensive skin-burns to be much richer in corpuscles and poorer in plasma than normal blood. This thickening of the blood is accounted for by the transudation of lymph at the burnt places, and is perhaps the primary cause of all the symptoms and of death.

We thus see that there is no real ground for assuming that any gaseous products are excreted by the human skin. Our knowledge of the chemistry of cutaneous activity is altogether very limited. Nothing certain is known concerning the chemical composition of perspiration,[5] and there is at present no reason for considering this secretion to have any other use than that of the purely physical action in regulating the temperature of the body. The evaporation of water on the surface of the body is the most effectual means of cooling it. It must not be forgotten what an enormous amount of heat becomes latent when

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[1] Max Schultze, *Arch. f. mik. Anat.*, vol. i. p. 26: 1865.

[2] Wertheim, *Wiener med. Presse*, No. 13: 1868; Ponfick, *Berl. klin. Wochenschr.*, No. 46: 1877; *Centralbl. f. d. med. Wissensch.*, Nos. 11, 16: 1880; von Lesser, Virchow's *Arch.*, vol. lxxix. p. 248: 1880.

[3] Hoppe-Seyler, *Zeitschr. f. physiol. Chem.*, vol. v. pp. 1, 344: 1881.

[4] Tappeiner, *Centralbl. f. d. med. Wissensch.*, vol. xix. pp. 385, 401: 1881.

[5] *Vide* O. Funke, Moleschott's *Unter. z. Naturlehre d. Menschen u. der Thiere*, vol. iv. p. 36: 1858; and W. Leube, "Ueber den Antagonismus zwischen Harn- und Schweissecretion und dessen therapeutische Bedeutung," *Deutsch. Arch. f. klin. Med.*, vol. vii. p. 1: 1870. An account of the previous literature is also given. Compare also A. Kast, "Ueb. aromatische Fäulnissprodukte im menschlichen Schweisse," *Zeitschr. f. physiol. Chem.*, vol. xi. p. 501: 1887. P. Argutinsky, Pflüger's *Arch.*, vol. xlvi. p. 594: 1890; E. Cramer, *Arch. f. Hygiene*, vol. x. p. 231: 1890.

water passes from the liquid to the gaseous state. The secretion of perspiration is entirely absent in many animals, as in the dog, and is replaced by a more copious evaporation from the surface of the lungs.

Before concluding the chapter on respiration and the behavior of gases in the body, we must consider the gases which occur in the alimentary canal, their origin, and their behavior under physiological and pathological conditions.

The GASES in the ALIMENTARY CANAL arise from four sources: (1) Atmospheric air is continually being swallowed with the saliva, with food and drink; part of it escapes again by the esophagus, but the rest passes into the intestine; (2) gases arise by fermentative processes in the contents of the stomach and intestine; (3) gases diffuse from the tissues of the intestinal wall into the intestine; and (4) CO_2 is liberated when the sodium carbonate of the intestinal juice is neutralized.

The following gases have, up to the present, been detected in the alimentary canal of human beings and of mammals:[1] O, N, CO_2, H, CH_5, H_2S.

Oxygen reaches the alimentary canal only by the air that is swallowed, and disappears almost entirely in the stomach, partly by uniting with the reducing substances which proceed from the fermentative processes already set up in the stomach, and especially with the nascent hydrogen arising from butyric acid fermentation, and partly by diffusion into the tissues of the gastric wall. Traces of oxygen could still be found in the gases obtained from the upper portion of the intestine, but none in that from the lower parts. Planer injected atmospheric air into a ligatured small intestine of a living dog, and even after one and a half hours, half of the oxygen had disappeared from the air and had been replaced by carbonic acid. In the case of a few fish, the diffusion of the atmospheric oxygen swallowed by them through the walls of the alimentary canal, plays an important part in the process of respiration.[2]

Nitrogen also reaches the alimentary canal with the air swallowed, but does not diffuse into the tissues of the intestinal wall, because the partial pressure of the nitrogen is very nearly the same in this latter as in atmospheric air. It must, on the

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[1] Planer, *Sitzungsber. d. k. Akad. d. W. zu Wien.*, vol. xlii. p. 307: 1860; E. Ruge, *ibid.*, vol. xliv. p. 739: 1862; C. B. Hofmann, *Wiener med. Wochenschr.*, 1872; Tappeiner, *Zeitschr. f. physiol. Chem.*, vol. vi. p. 432: 1882; *Zeitschr. f. Biolog.*, vol. xix. p. 228: 1883; and vol. xx. p. 52: 1884; *Arbeit. a. d. pathol. Inst. z. München.*, edit. by Bollinger, pp. 215, 226: Stuttgart, 1886.

[2] Erman, *Ann. d. Physik*, vol. xxx. p. 113: 1808; Leydig, *Arch. f. Anat. u. Physiol.*, p. 3: 1853; Baumert, "Chemische Untersuchung über die Respiration des Schlammpeitzgers": Breslau, 1855.

contrary, be assumed that nitrogen diffuses out of the tissues of the intestinal wall into the intestine. This occurs in the lower portion of the intestine, in proportion as other gases are developed by fermentation and the partial pressure of the nitrogen sinks. The intestinal gases as a matter of fact always contain an abundance of nitrogen.

Hydrogen is formed in large quantities by fermentative processes, and especially, together with CO_2, in butyric acid fermentation. This latter form of fermentation can always be detected in the contents of the large and small intestine.[1] As already mentioned, marsh-gas arises, with carbonic acid, by the decomposition of cellulose. But these are not the only two processes of fermentation by which CO_2, H, and CH_4 are formed in the intestine. Ruge found marsh-gas in the gases of the colon of living people, even after a diet exclusively composed of meat; and Tappeiner found abundance of marsh-gas and hydrogen in the gases of pigs' colons, after they had been fed for three weeks entirely on meat. These gases proceed not only from the decomposition of carbohydrates, but also of proteids. Kunkel[2] found that the gases produced by artificial pancreatic digestion, without excluding the fermentative organisms, contained as much as 60 per cent. H, and 1.6 per cent. marsh-gas; and Tappeiner[3] showed that sterilized solutions of common salt with peptone and fibrin, when mixed with a little of the intestinal contents, developed a mixture of gases which contained as much as 40 per cent. H, and as much as 19 per cent. CH_4. It is noteworthy that in one of these experiments Tappeiner produced from a solution of peptone a mixture of gases which contained 99.65 per cent. CO_2, as well as 0.14 H and 0.21 CH_4. In the intestine fermentations appear to go on in which carbonic acid alone, without any other gas, is developed from proteid.

Besides this, carbonic acid is developed in large quantity through the neutralization of the acid chyme by the sodium carbonate of the intestinal juice. If we may assume for human beings the same proportion of hydrochloric acid in the gastric juice which was found by Carl Schmidt in the dog, it would appear that 6 liters of CO_2 are daily liberated in our intestine by neutralization of the hydrochloric acid. We have to add the still larger quantity set free by the neutralization of lactic and butyric acids, which are constantly formed

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[1] Compare Rubner, *Zeitschr. f. Biolog.*, vol. xix. p. 84, *et seq.:* 1883.

[2] Kunkel, *Verhandl. d. physik.-med. Gesellsch. in Wurzburg*, N. F., vol. viii. p. 134: 1874.

[3] Tappeiner, *Arb. a. d. patholog. Inst. in München*, vol. i. p. 218: 1886.

in the intestine from the carbohydrates of food. Still, we are not inconvenienced by these large volumes of CO_2, for the coefficient of absorption of carbonic acid is very high, and the partial pressure of CO_2 in the intestinal walls is scarcely ever higher than 10 per cent. of an atmosphere. Therefore, as soon as the bowel contains more than 10 per cent. of CO_2, diffusion into the blood must commence. The proportion of carbonic acid in intestinal gases is commonly from 20 to 50 per cent., and more. It follows that there is constantly an active current of carbonic acid from the intestine into the blood. In the experiments on dogs with duodenal fistulæ, Mering has shown that the absorption of CO_2 begins even in the stomach. The CO_2 developed in the bowel is exhaled by the lung.

On the other hand, hydrogen may give rise to much discomfort, owing to its very low coefficient of absorption. It follows that patients suffering from chronic dyspepsia and disposed to flatulence, must be extremely careful to avoid such articles of diet as tend to a butyric fermentation. According to the observations of Ruge and Tappeiner, milk appears to be especially injurious in this respect. The experience of many patients coincides with this view. In the same way starchy foods, which are hard to digest, are to be avoided, because they convey large quantities of carbohydrates into the lower portion of the small intestine, the alkalinity of which encourages butyric fermentation. It would be wise to administer carbohydrates in the form of stewed fruits, because we thus convey with them acids into the bowels and because the acids prevent butyric fermentation. There are many patients with whom cereals, the leguminosæ, and potatoes disagree, but who are able to take stewed fruits with rice, which is easily digested and which is manifestly almost entirely absorbed in the upper part of the bowel.

The following table gives the coefficients of absorption of the intestinal gases. They have been determined by Bunsen at a temperature of 15° C. It is to be regretted that they have not also been determined for the body-temperature.

Nitrogen	0.01478	CH_4	0.03909
Hydrogen	0.01930	CO_2	1.0020
Oxygen	0.02989	H_2S	3.2326

The amount of sulphuretted hydrogen contained in the intestinal gases is very small, and cannot be quantitatively determined. It is however conceivable that the amount developed in the bowel is sometimes larger than might be supposed from the small amount contained in the intestinal gases. We must not forget how high the coefficient of absorption of sulphuretted hydrogen is, being one hundred times higher than that of oxygen which is so easily diffusible. Sulphuretted hydrogen, in proportion as it is set free, must at once diffuse into the blood. Planer injected into the rectum of dogs sulphuretted hydrogen diluted with hydrogen, and observed toxic symptoms within one or two minutes. When, in certain processes of disease, abnormal decomposition takes place in the contents of the bowel, it is possible that a large quantity of sulphuretted hydrogen may be developed. In the artificial digestion of fibrin by pancreatic juice, without excluding bacteria, Kunkel found that the gases contained as much as 1.9 per cent. of H_2S. It is possible that in the headache, vertigo, and nausea frequently accompanying gastric and intestinal catarrh and persistent constipation, poisoning by sulphuretted hydrogen plays a part. Senator[1] communicates the following case, which he regards as undoubtedly one of poisoning by sulphuretted hydrogen. He succeeded in finding sulphuretted hydrogen in the urine of a patient suffering from acute intestinal catarrh, as it distinctly gave a brown color to a visiting-card which contained lead. The eructations of the patient caused a distinct odor of sulphuretted hydrogen. He also had repeated attacks of vertigo, accompanied by epigastric oppression and a dark complexion. It is stated that persons engaged in the emptying of cesspools, and exposed to sulphuretted hydrogen gas, have experienced similar symptoms.

We have at present little certain knowledge as to what becomes of the absorbed hydrogen and marsh-gas. They either become oxidized or reappear in the exhaled air. An experiment made in Zuntz's[2] laboratory in Berlin, with a tracheotomized rabbit showed that the air exhaled by these animals invariably contains hydrogen, and generally marsh-gas as well—to a greater extent even than the gases voided during the same period *per anum*. It has not yet been determined whether all hydrogen and all marsh-gas which are absorbed from the intestine reappear in the expired air, or whether a part is oxidized in the body. The decision of this question would be of great interest for the theory of internal respiration. (Compare p. 238.)

The quantitative composition of intestinal gases necessarily

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[1] Senator, *Berlin. klin. Wochensch.*, Jahrg. v. p. 254: 1868.

[2] B. Tacke, "Ueber die Bedeutung der brennbaren Gase im thierischen Organismus," Inaug. Dissert.: Berlin, 1884. Also *Ber. d. deutsch. chem. Ges.*, vol. xvii. p. 1827: 1884.

varies greatly according to the diet and the condition of the entire digestive apparatus, and especially according to the extent to which fermentation can be resisted. Thus for instance Ruge found in the intestinal gases of the same person :—

	After milk diet.	After four days' diet of leguminosæ only.	After three days' diet of meat only.
Oxygen	—	—	—
Nitrogen	36.71	18.96	64.41
Hydrogen	54.23	4.03	0.69
CH_4	—	55.94	26.45
CO_2	9.06	21.05	8.45
H_2S	—	Trace	—

Tappeiner[1] found that the gases removed half an hour after death from the corpse of a man who had been executed, exhibited the following composition :

	Stomach.	Ileum.	Colon.	Rectum.
Oxygen	9.19	67.71	—	—
Nitrogen	74.26		7.46	62.76
Hydrogen	0.08	3.89	0.46	—
CH_4	0.16	—	0.06	0.9
CO_2	16.31	28.4	91.92	36.4

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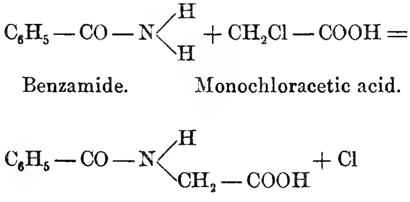
[1] Tappeiner, *Arb. a. d. patholog. Inst. d. München*, vol. i. p. 226 : 1886.

LECTURE XIX

THE NITROGENOUS END-PRODUCTS OF METABOLISM —HIPPURIC ACID, UREA, CREATIN

THE examination of the processes of respiration has shown us that the bulk of the carbon is eliminated from our body by the lungs as carbonic acid. The remainder of the carbon takes a different course. It quits our body in combination with the bulk of the nitrogen, in the form of a series of compounds very rich in nitrogen, through the kidneys. Among these nitrogenous end-products the chief in man are urea, uric acid, hippuric acid, creatin, and creatinin. A considerable portion of nitrogen appears in urine as an inorganic compound—as a salt of ammonia.

We will now pursue the origin of these end-products in the animal body as far as the present state of our knowledge permits. We will begin with HIPPURIC ACID, because the origin of this compound has been more carefully studied and is better known than that of any of the other nitrogenous end-products. The constitution of hippuric acid is accurately known. The following mode of preparation makes it very clear :—



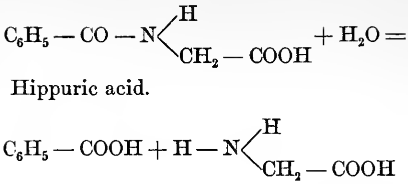
$$C_6H_5 - CO - N\begin{cases} H \\ H \end{cases} + CH_2Cl - COOH =$$

Benzamide. Monochloracetic acid.

$$C_6H_5 - CO - N\begin{cases} H \\ CH_2 - COOH \end{cases} + Cl$$

Hippuric acid.

If we boil hippuric acid with strong mineral acids or with alkalies, or subject it to the action of ferments, it splits up with hydration into benzoic acid and amido-acetic acid (glycocol).



$$C_6H_5-CO-N\begin{cases}H\\ CH_2-COOH\end{cases} + H_2O =$$

Hippuric acid.

$$C_6H_5-COOH + H-N\begin{cases}H\\ CH_2-COOH\end{cases}$$

Benzoic acid. Glycocol.

Hippuric acid is again formed with dehydration, from these two products of its decomposition, if they are allowed to act upon one another at a high temperature and under increased pressure. To effect this they are inserted dry into a glass tube, the ends of which are fused, and the tube is kept at a temperature of 160° C. for twelve hours.[1]

Hippuric acid is also formed in the animal body by the combination of benzoic acid and glycocol. If benzoic acid is introduced into the stomach of an animal or a human being, it reappears as hippuric acid in the urine. Doubtless the glycocol used in its formation arises from the decomposition of the proteids of the tissues. Free glycocol has certainly not as yet been proved to exist in animals. As little are we able to obtain it by the artificial decomposition of proteid, but we know that the immediate derivatives of proteid, the collagenous substances, when decomposed either by ferments, by acids or by alkalies, readily yield glycocol. In combination with an acid glycocol also appears, as we have seen, in bile as glycocholic acid.

Hippuric acid is also constantly found in the urine of the herbivora, without the artificial administration of benzoic acid. The numerous aromatic compounds which are contained in the tissues of plants, and which in the animal body are converted by oxidation into benzoic acid, evidently yield the material for its formation. However, small quantities of hippuric acid may be found in the urine of dogs fed only upon meat, and also during inanition.[2] In this case the benzoic acid is formed from the aromatic radicals which are contained in the proteid molecule.[3]

The amount of hippuric acid contained in the urine of man in twenty-four hours is generally less than 1 grm.; but after

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[1] Dessaignes, *Journ. Pharm.*, vol. xxxii. p. 44: 1857.

[2] E. Salkowski, *Ber. d. deutsch. chem. Ges.*, vol. xi. p. 500: 1878.

[3] E. and H. Salkowski, *ibid.*, vol. xii. pp. 107, 648, 653: 1879; *Zeitschr. f. physiol. Chem.*, vol. vii. p. 161: 1882; E. Salkowski, *Zeitschr. f. physiol. Chem.*, vol. ix. p. 229: 1885. Compare also Tappeiner, *Zeitschr. f. Biolog.*, vol. xxii. p. 236: 1886; and R. Baas, *Zeitschr. f. physiol. Chem.*, vol. xi. p. 485: 1887.

the consumption of certain berries and fruits it amounts to several grammes.

The fact that benzoic acid introduced into the stomach reappears as hippuric acid in the urine was discovered as early as 1824 by Wöhler.[1] This discovery was afterwards confirmed by numerous experiments, and excited some attention, for it was the first synthetic process which was proved to occur in the animal body. Since then a long series of other syntheses have been discovered in the animal body. I need only remind my readers of the formation of the conjugated sulphuric acids and glycuronic acids, and of the formation of glycogen from sugar. It is probable that the formation of proteid from peptone belongs to this category. We shall soon become acquainted with other synthetic processes.

There are two reasons why these synthetic processes in the animal body have excited the interest of physiologists and chemists during the last twenty years: in the first place, these facts were in contradiction to the dominant doctrine of Liebig with regard to the universal contrast between the metabolic processes in plants and in animals; in the second place, the syntheses in animals are an unsolved problem to chemists, although it is the rapid progress in our knowledge of the syntheses of organic compounds which constitutes the greatest triumph of modern chemistry. We are already able artificially, to build up, atom for atom, out of their elements, a series of organic compounds, some of a very complex character. We no longer doubt that all the rest, even the most complex, will be thus produced; it is merely a question of time. Still, this in no way represents the synthetic processes in the living cell, for all our artificial syntheses can only be achieved by the application of forces and agents which can never play a part in vital processes, such as extreme pressure, high temperature, strong galvanic currents, concentrated mineral acids, free chlorin—factors which are immediately fatal to a living cell.

Thus we have seen that the artificial synthesis of benzoic acid and glycocol to hippuric acid could only be induced by heating both substances in a dry condition, in a closed tube, to a temperature of 160° C. This implies extreme pressure, extreme temperature, and absence of water. The very reverse is the case in the animal body, where we find water in every tissue, and the ordinary atmospheric pressure and temperature in every cell. Even cold-blooded animals form hippuric acid. It follows that the animal body has command of ways and

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[1] Berzelius, "Lehrbuch der Chemie," translated by Wöhler, vol. iv. p. 376; Vote. Dresden, 1831.

means of a totally different character, by which the same object is achieved. An inquiry into these would be of extreme interest to the chemist and to the physiologist; the former would thus obtain new methods for rising to still more complicated combinations, and the physiologist would be enabled to explain many of the most obscure processes in metabolism.

For this reason, Schmiedeberg and I conjointly[1] resolved to study the conditions under which the synthesis of hippuric acid takes place in the animal body.

In order to be able to trace benzoic and hippuric acids through the tissues of the animal body, we required above all, a precise method for their detection and estimation. This we succeeded in obtaining after many experiments. We now possess a method[2] which enables us to separate these acids from all other constituents of the animal body, and to weigh them in a pure crystalline form without any appreciable loss.

We had next to determine in what organs and in what tissues the synthesis takes place. We naturally thought first of the liver. It is known that here another acid, conjugated with glycocol (glycocholic acid), is formed; besides, synthetic processes have often been assigned to the liver. If this view were correct, the removal of the liver must cause the benzoic acid introduced into the blood to circulate unaltered in it, and to pass out by the kidneys unchanged.

This experiment could not be carried out in mammals because, after ligature of the hepatic vessels, the bulk of the blood accumulates in the portal system, and the circulation in the other organs is almost entirely arrested. Dogs die from thirty to fifty minutes after this operation. It may be said that they begin to die as soon as the portal vein is tied.

We therefore instituted our experiments on frogs. They bear the extirpation of the liver very well, surviving the operation for three or four days. They run about during this time with almost undiminished vigor. If we introduced benzoic acid into the dorsal lymphatic sac, the frogs invariably formed hippuric acid, which was more copious when, in addition to benzoic acid, glycocol was injected. Unless benzoic acid was injected, no trace of hippuric acid was ever to be found in the tissues or in the secretions of the frog. It follows of necessity that the liver is not the locality, at all events not the exclusive locality, for the formation of hippuric acid.

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[1] Bunge and Schmiedeberg, *Arch. f. exper. Path. u. Pharm.*, vol. vi. p. 233: 1876.

[2] The method is described, *loc. cit.*, pp. 234–239.

We then thought that the synthesis might possibly occur in the kidney. In order to decide this, it was necessary to have recourse to warm-blooded animals. Dogs survive the ligature of the vessels of both kidneys for several hours, and the circulation in their other organs is not materially affected. We injected glycocol and benzoic acid into the blood of dogs thus operated upon, bled them to death after three or four hours, and examined the blood of the liver and muscles for hippuric acid without ever finding a trace of it; we found only benzoic acid. It therefore appears that all the other organs together cannot, without the kidneys, combine glycocol and benzoic acid, and that the kidney is the locality in which the synthesis is performed.

A sceptical critic will not be satisfied with this conclusion. There is still room for objection. The ligature of the kidneys may be regarded as so violent an operation as to produce direct and indirect disturbances of all kinds in all parts of the organism. We must therefore admit the possibility that disturbances may be produced in tissues with which we are as yet unacquainted, and in which the synthesis is effected.

The hope remained that if we could show that the kidney, separated from other organs, was able to produce the synthesis by itself, we should be in a position to prove that the formation of hippuric acid took place in that organ. This hope was realized. We bled a dog to death, removed the kidneys, added glycocol and benzoic acid to the defibrinated blood, and conveyed it, under an approximately normal pressure, through the artery, and allowed it to flow out of the veins of one of the kidneys. The blood that passed out of the vein was returned to the reservoir, from which it reëntered the artery; and this process was continued for several hours. Hippuric acid was invariably found in the blood after its passage through the kidney, and in the fluid which during its passage escaped by the ureter. But in the other kidney, and in a portion of the blood which had not traversed the kidney, no trace of hippuric acid could at any time be discovered. It follows that hippuric acid was formed in the excised kidney.[1]

If we added benzoic acid without glycocol to the blood that was passed through the kidney, the quantity of hippuric acid formed was small; but it was considerable when glycocol was mixed with it. As a matter of fact, the two ingredients had entered into combination, with separation of water. It was indifferent whether we raised the temperature of the

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[1] Wilh. Kochs has confirmed these results by a series of careful experiments in Pflüger's laboratory (Pflüger's *Arch.*, vol. xx. p. 64: 1879).

kidney and the blood to the temperature of the body, or cooled it to that of the room. In either cases the synthesis was effected. It was remarkable how long the excised kidney retained the faculty of forming hippuric acid. In one of our experiments we allowed the kidney to remain for forty-eight hours in an ice-chest. We passed the blood of another dog through it, which had been obtained twenty-four hours previously; nevertheless some hippuric acid was formed.

We now inquired whether the living tissue of the kidney is essential for the synthesis. Does the result depend upon the formed elements and upon a definite histological arrangement, or is this function of the kidney only due to its containing certain chemical substances? In the latter case, it might be possible to isolate these substances, and then to effect the synthesis artificially.

Accordingly we destroyed the renal tissue. We chopped up the kidney and pounded it into a homogeneous pulp. To this we added blood, glycocol, and benzoic acid, and allowed the mixture to stand, shaking it at frequent intervals. We varied the experiment, applied different temperatures, provided a copious supply of oxygen, but we never succeeded in finding a trace of hippuric acid.

This experiment was repeated in Pflüger's laboratory by Kochs.[1] When the kidney had only been chopped up, Kochs discovered minute traces of hippuric acid, but if it had been not only chopped up, but also rubbed up "in a mortar with large pieces of glass" to an almost homogeneous mass, not a trace of hippuric acid was to be found; nor was it met with when the kidney, before being chopped up, had been frozen at − 20° C., and thawed at 40°.

These experiments appear to prove that the synthesis is due to the living cells of the kidney, and not to one of its chemical components.

We now inquired whether the blood-corpuscles are essential for the production of the synthesis. We therefore conducted serum which had been deprived of all cells by the centrifugal machine, together with glycocol and benzoic acid, through the excised kidney. In this case no hippuric acid was formed. It follows that the blood-corpuscles also take an active part in the synthesis.

We now proceeded to inquire into the part played by the blood-cells in this process, and to determine whether they act only as oxygen-carriers.

In order to decide this question, Schmiedeberg and Arthur

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[1] Wilhelm Kochs, Pflüger's *Arch.*, vol. xx. p. 70, *et seq.*: 1879.

Hoffman[1] conducted blood mixed with glycocol and benzoic acid, and in which the oxygen had been replaced by carbonic oxid, through the kidneys. The result was that no hippuric acid was formed. The blood-cells therefore also act as oxygen-carriers in the synthetic process, but whether they have only this function remains uncertain. It may be objected that the carbonic oxid, besides driving out the oxygen, has a toxic effect on the renal cells. The following experiment of Schmiedeberg and Hoffman goes to prove that certain poisons do deprive the cells of the power of effecting syntheses. They conducted blood, to which, besides glycocol and benzoic acid, quinine had been added, through the kidneys. Only a very small quantity of hippuric acid was subsequently found. It is known, from the investigations of C. Binz,[2] that quinine arrests the ameboid movements of the cells. The same influence that kills the cell likewise deprives it of the capability of bringing about syntheses.

With regard to the locality where hippuric acid is formed in the animal body, I would add that its exclusive formation in the kidney is only proven in the case of the dog. Schmiedeberg and I have already shown that frogs form hippuric acid even after extirpation of the kidney. Salomon[3] discovered subsequently that certain mammals do not form hippuric acid exclusively in the kidney. Salomon, after giving benzoic acid to rabbits which had been deprived of their kidneys, found abundant hippuric acid in their blood, muscles, and liver.

If benzoic acid be introduced into birds, it appears in the urine, not as hippuric acid, but combined with a base, which Jaffé[4] described as ornithin, having the formula $C_5H_{12}N_2O_2$. It is probably diamido-valerianic acid. Two other diamido-acids were discovered later by Drechsel among the products of disintegration of proteids, *viz.*, diamido-acetic acid and diamido-caproic acid or lysin. These latter have hitherto been obtained only outside the organism by the artificial hydrolysis of proteids, whereas diamido-valerianic acid has only been detected as the result of the natural decomposition of proteids in the body. The compound of benzoic acid and ornithin has been called ornithuric acid by Jaffé.

But, as already mentioned, a very inconsiderable portion of the nitrogen in human beings is eliminated as hippuric acid. The bulk of it, in man and mammals, appears in the urine as

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[1] Arthur Hoffman, *Arch. f. exper. Path. u. Pharm.*, vol. vii. p. 239: 1877.

[2] C. Binz, *Arch. f. mikr. Anat.*, vol. iii. p. 383: 1867.

[3] Salomon, *Zeitschr. f. physiol. Chem.*, vol. iii. p. 365.

[4] Jaffé, *Ber. d. deutsch. chem. Ges.*, vol. x. p. 1925: 1877; vol. xi. p. 406: 1878. Hans Meyer, *ibid.*, vol. x. p. 1930: 1877.

UREA. The amount of urea excreted is therefore regarded as an index of the consumption of proteid in the body. The greater portion of nitrogen is introduced in the form of proteid. Nearly half the weight of urea consists of nitrogen. The 100 grms. of proteid daily used up by one person contain about 16 grms. of nitrogen, to which 34 grms. of urea correspond. This is about the quantity found in a man's urine during twenty-four hours.

The constitution of urea is known. Its formation from carboxyl chlorid ($COCl_2$) and ammonia, as well as from ethyl carbonate and ammonia, undoubtedly shows that urea should be regarded as the amid of carbonic acid, carbamid $[CO(HN_2)_2]$. On heating with acids or alkalies or by the action of ferments, urea takes up two molecules of water and is converted into carbonate of ammonia. Urea is a neutral compound, capable of crystallization and very readily soluble in water.

How does urea arise from proteid, and what are the intermediate stages? A recapitulation of our previous remarks on the changes of proteid in the body may not be out of place here. It was shown that proteid was converted by the digestive ferments into peptones; that the peptones are probably products of decomposition; and that, by continued action of the digestive ferments or of other ferments of decomposition, a part of the nitrogen is split off in the form of amido-acids, as amido-caproic acid or leucin $[C_5H_{10}(NH_2)COOH]$, as tyrosin, an aromatic amido-acid $\left(C_6H_4\left\{\begin{array}{l}OH\\C_2H_3(NH_2)COOH\end{array}\right.\right)$, and as amido-succinic acid or aspartic acid[1] $[C_2H_3(NH_2)(COOH_2)]$ and its homologue, glutamic acid, $C_3H_5(NH_2)(COOH)_2$. The proteids also give the same products of decomposition on boiling with acids or with alkalies.[2] We have moreover seen that a portion of the proteids is converted in the animal body into collagenous substances which, under the same conditions as the proteids, produce amido-acids, and especially leucin and glycocol.[3]

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[1] Radziejewski and E. Salkowski, *Ber. d. deutsch. chem. Ges.*, vol. vii. p. 1050: 1874; W. von Knieriem, *Zeitschr. f. Biolog.*, vol. xi. p. 198: 1875.

[2] Hlasiwetz and Habermann, *Ann. d. Chem. u. Pharm.*, vol. clxix. p. 150: 1873: E. Schulze, J. Barbieri und E. Bossard, *Zeitschr. f. physiol. Chem.*, vol. ix. p. 63: 1884; E. Schulze und E. Bossard, *ibid.*, vol. x. p. 134: 1885; M. P. Schützenberger, *Bull. de la Société chim.*, vol. xxiii. pp. 161, 193, 216, 242, 385, 433; vol. xxiv. pp. 2, 145: 1875; vol. xxv. p. 147: 1876; Schützenberger et A. Bourgeois, *Compt. rend.*, vol. lxxxii. p. 262: 1876. Compare also R. Maly, *Sitzungsber. d. k. Akad. d. W. in Wien.*, Math. nat. Cl., vol. xci. part ii., Feb., 1885; vol. xcvii. part ii., March, 1888; and vol. xcix. part ii., Jan., 1889.

[3] Nencki, "Ueber die Zersetzung der Gelatine und des Eiweisses bei der Fäulniss mit Pankreas": Berlin, 1876. Jules Jennaret, *Journ. f. prakt. Chem.*, N. F., vol. xv. p. 353: 1877 (from Nencki's laboratory).

More recently a number of basic substances have been discovered among the products of disintegration of proteids. As we have already mentioned, Drechsel found diamido-acetic acid,[1] diamido-caproic acid or lysin,[2] and a body to which he gave the name of lysatin and which has been since found to consist of a mixture of lysin with another base, arginin.[3] This substance, together with histidin,[4] was first discovered by Hedin.

Arginin ($C_6H_{14}N_4O_2$) and histidin ($C_6H_9N_3O_2$) had already been discovered by Kossel, together with lysin, among the decomposition products of certain bases which occur in the spermatozoa of certain fish. Miescher[5] had previously found a base of the composition $C_{16}H_{28}N_9O_2$ in the spermatozoa of Rhine salmon and had given it the name of protamin. Kossel[6] found similar bases in the spermatozoa of other Salmonidæ as well as of the sturgeon and herring. It is remarkable that the protamins give the most constant proteid reaction, *viz.*, the biuret reaction.

These facts suggest that all these nitrogenous substances might be regarded as the precursors of urea. So far only the amido-acids have been the subject of direct experiment. Schultzen and Nencki[7] administered leucin and glycocol to dogs, and found that these compounds did not reappear in the urine, but that there was a corresponding increase of urea. Salkowski,[8] on repeating these experiments, fully confirmed these results. Knieriem[9] showed, by a similar method of research, that aspartic acid is also converted into urea.

But even these facts tend but little to the elucidation of the origin of urea. It is only the smallest part of urea which can be formed from amido-acids. This is seen by a glance at the empirical formula of proteids. We have shown (pp. 49–51) that

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[1] E. Drechsel, *Ber. d. k. säch. Ges. d. Wissensch.*, p. 115: 1892.

[2] E. Drechsel and R. Krüger, *Ber. d. deutsch. chem. Ges.*, vol. xxv. p. 2454: 1892.

[3] Hedin, *Zeitschr. f. physiol. Chem.*, vol. xx. p. 186: 1895; vol. xxi. p. 155: 1896. Compare also E. Schulze and E. Steiger, *ibid.*, vol. xi. p. 43: 1887.

[4] Hedin, *Zeitschr. f. physiol. Chem.*, vol. xxii. p. 191: 1896. Compare M. Bauer, *ibid.*, vol. xxii., p. 284: 1896.

[5] Miescher, *Verhandl. d. naturf. Ges. in Basel*, p. 138: 1874. J. Piccard, *Ber. d. deutsch. chem. Ges.*, vol. vii. p. 1714: 1874. Posthumous paper of Miescher, edited by O. Schmiedeberg, *Arch. f. exper. Path. u. Pharm.*, vol. xxxvii. p. 100: 1896.

[6] Kossel, *Sitzungsber. d. Ges. z. Beförd. d. ges. Naturwissensch. z. Marburg*, No. 5, p. 56: July, 1897.

[7] Schultzen and Nencki, *Zeitschr. f. Biolog.*, vol. viii. p. 124: 1872.

[8] E. Salkowski, *Zeitschr. f. physiol. Chem.*, vol. iv. p. 100: 1879.

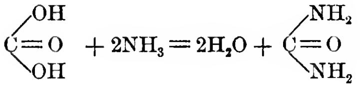
[9] W. von Knieriem, *Zeitschr. f. Biolog.*, vol. x. p. 279: 1874.

the following formulæ may be deduced from the most reliable analyses of the purest preparations of proteids.

Egg-albumin.	$C_{204}H_{322}N_{52}O_{66}S_2$.
Proteid in hemoglobin from horse.	$C_{680}H_{1098}N_{210}O_{241}S_2$.
Proteid in hemoglobin from dog.	$C_{726}H_{1171}N_{194}O_{214}S_3$.
Globulin from pumpkin seeds.	$C_{292}H_{481}N_{90}O_{83}S_2$.

We see that there is not nearly sufficient carbon in the proteid to permit of all the nitrogen issuing as an amido-acid. In the various kinds of proteid, from three to four atoms of carbon go to one atom of nitrogen; in aspartic acid, four atoms of carbon to one of nitrogen; in leucin, six; and in tyrosin, as many as nine. Glycocol indeed contains only two atoms of carbon to one of nitrogen. But it is questionable whether it is this amido-acid which is formed in especially large quantity from the proteid in the animal body. As stated, it cannot be obtained from the proteid outside the organism, but only if the proteid has been previously changed by the vital process in the animal into a collagenous substance; and it is only the smallest portion of the proteid of the food which undergoes this conversion. It must also be taken into consideration that the proteid in the animal body also yields products of decomposition free from nitrogen and very rich in carbon. What follows will make it apparent that fat and glycogen can be formed in the animal body from proteid. We are thus obliged to conclude that the largest portion of the nitrogen is split off from the proteid molecule as a compound containing very little carbon.

It is possible that a part of the urea in the animal body is separated directly from the proteid as a neutral compound. But it is also possible that ammonia and carbonic acid split off from the proteid, subsequently combining, with elimination of water, to form urea. This would be a process completely analogous to that involved in the formation of hippuric acid. As monobasic benzoic acid unites with a molecule of a substituted ammonia (glycocol), losing one molecule of water, to form hippuric acid, so dibasic carbonic acid unites with two molecules of ammonia, losing two molecules of water, to form urea—



$$C{=}O\begin{smallmatrix}\diagup OH\\ \diagdown OH\end{smallmatrix} + 2NH_3 = 2H_2O + C{=}O\begin{smallmatrix}\diagup NH_2\\ \diagdown NH_2\end{smallmatrix}$$

The conversion of the amido-acids into urea may be thus represented: they are first split up and oxidized into carbonic acid and ammonia, and in this state yield the material for the formation of urea. In any case, we have to deal with another synthetic process, for the leucin and glycocol contain but one atom of nitrogen in the molecule, whereas urea has two.

The supposition that carbonate of ammonia was the antecedent of urea was based upon the following observations of Buchheim and his pupil Lohrer.[1] The latter took 3 grms. of ammonia in the form of citrate, expecting that it would behave in the body like citrate of potash or soda, which are known to pass into the urine as carbonates of potash or soda, and to render the urine alkaline. But this did not happen. The urine remained acid. The carbonate of ammonia formed must therefore have been converted into a neutral compound. It was readily assumed that urea had been formed.

In order to decide the question whether ammonia is converted in the animal body into urea, careful experiments on the metabolic changes were made by Knieriem[2] on dogs and on human beings, and by Salkowski[3] on dogs and on rabbits. The experiments made on rabbits gave results which were quite definite: after the administration of chlorid of ammonia, the excretion of ammonia was scarcely increased at all, whereas that of urea was increased. The experiments on human beings and on dogs were not so definite. Part of the ammonia appeared unaltered in the urine, and it remained doubtful whether the extra excretion of urea was to be ascribed to the ammonia administered, or to an indirect increase of proteid-decomposition produced by the ammonia. This difference in its action in rabbits as compared with human beings and dogs may be explained as follows. The hydrochloric acid of the chlorid of ammonia introduced, by its strong affinity for ammonia, prevents the union of the latter with the carbonic acid to form urea. Now, in the organism of herbivora this hindrance is overcome, because the vegetable food yields an alkaline ash; carbonate of potash is also formed in the organism by combustion; this, together with the chlorid of ammonia, is converted into chlorid of potash and carbonate of ammonia, which latter is changed into urea. The mixed diet of human beings and of dogs in Knieriem's and Salkowski's experiments would necessarily give a feebly acid ash; the conversion of the ammonia into urea was therefore not so

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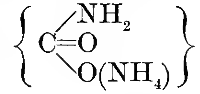
[1] Julius Lohrer, "Ueber den Uebergang der Ammoniaksalze in den Harn," Inaug. Dissert. Dorpat, 1862, pp. 36, 37.

[2] von Knieriem, *Zeitschr. f. Biolog.*, vol. x. p. 263: 1874.

[3] E. Salkowski, *Zeitschr. f. physiol. Chem.*, vol. i. p. 1: 1877.

complete. Feder,[1] who experimented with chlorid of ammonia upon fasting dogs, recovered all the ammonia from the urine. For the fasting dog is nourished by some of the proteid of its tissues, and a great deal of sulphuric acid is set free. This prevents the ammonia from uniting with the carbonic acid. Fr. Walter[2] and Coranda[3] showed the excretion of ammonia to be considerably augmented in dogs and in man after the administration of hydrochloric acid. The latter impedes the normal formation of urea. The administration of carbonate of soda diminishes the normal excretion of ammonia.[4] For this reason the experiments on the formation of urea were repeated in Schmiedeberg's laboratory,[5] but the ammonia was not administered in combination with strong mineral acids, but simply as carbonate. The dog swallowed the carbonate of ammonia wrapped in meat readily enough; in this manner 3 grms. NH_3 were administered to the animal on two successive afternoons. The excretion of ammonia in the urine was not found to be augmented, but there was an increase of urea, and the urine remained acid. Thus there can be no doubt that carbonate of ammonia is converted into urea.

Hoppe-Seyler[6] and Salkowski[7] have arrived at other views concerning the origin of urea. They regard cyanic acid as the immediate precursor of urea, and Drechsel[8] considers that urea arises from carbamate of ammonia. This last opinion is not at variance with the idea that urea originates in carbonate of ammonia. For carbamate of ammonia  $\left\{ C \begin{matrix} \diagup NH_2 \\ =O \\ \diagdown O(NH_4) \end{matrix} \right\}$ stands midway between carbonate

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[1] Feder, *Zeitschr. f. Biolog.*, vol. xiii. p. 256: 1877.

[2] Fr. Walter, *Arch. f. exper. Path. u. Pharm.*, vol. vii. p. 148: 1877.

[3] Coranda, *ibid.*, vol. xii. p. 76: 1880.

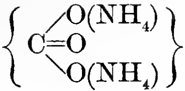
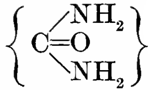
[4] Munk, *Zeitschr. f. physiol. Chem.*, vol. ii. p. 29: 1878; E. Hallervorden, *Arch. f. exper. Path. u. Pharm.*, vol. x. p. 124: 1879.

[5] Hallervorden, *loc. cit.*, whose results have been confirmed by Feder and Voit, *Zeitschr. f. Biolog.*, vol. xvi. p. 177: 1880.

[6] Hoppe-Seyler, *Ber. d. deutsch. chem. Ges.*, vol. vii. p. 34: 1874; and "Physiologische Chemie," pp. 809, 810: Berlin, 1881.

[7] E. Salkowski, *Centralbl. f. d. med. Wissensch.*, p. 913: 1875; *Zeitschr. f. physiol. Chem.*, vol. i. pp. 26–42: 1877. Compare also Schmiedeberg's objections in the *Arch. f. exper. Path. u. Pharm.*, vol. viii. p. 4, *et seq.:* 1878; and Schröder's, *ibid.*, vol. xv. pp. 399, 400: 1882.

[8] E. Drechsel, *Ber. d. sächs. Ges. d. Wissensch.*, p. 171: 1875; *Journ. f. prakt. Chem.*, N. F., vol. xii. p. 417: 1875; vol. xvi. pp. 169, 180: 1877; vol. xxii. p. 476: 1880. Compare also the objections raised by Franz Hofmeister, Pflüger's *Arch.*, vol. xii. p. 337: 1876. Considerable difficulties, which have not yet been successfully overcome, are met with in the attempt to detect and determine quantitatively the carbamic acid in the urine and tissues. Compare Hahn and Nencki, *Arch. d. Sc. biol.*, vol. i. p. 447: St. Petersburg, 1892.

of ammonia  $\left\{\mathrm{C}\begin{array}{l}\diagup\mathrm{O(NH_4)}\\=\mathrm{O}\\\diagdown\mathrm{O(NH_4)}\end{array}\right\}$ and urea  $\left\{\mathrm{C}\begin{array}{l}\diagup\mathrm{NH_2}\\=\mathrm{O}\\\diagdown\mathrm{NH_2}\end{array}\right\}$. By eliminating one molecule of water, carbonate of ammonia yields carbamate of ammonia; by elimination of a second molecule, urea. As it would lead me too far to enter into these theories at greater detail, I refer the reader to the interesting original works that deal with the matter.

The most complete and reliable researches as to the locality in which urea is generated have been made by W. von Schröder.[1] He extirpated both kidneys in a dog, and took a specimen of the blood from the carotid immediately after the operation. The dog was bled to death twenty-seven hours afterwards. The quantity of urea in each sample of blood was determined.[2] In the first case it amounted to 0.5 per thousand; in the second, to 2 per thousand. The urea in the blood is therefore increased fourfold by the extirpation of the kidneys, and it follows that the kidneys cannot be the only place where urea is formed.[3]

But the possibility still remained that urea was formed in the kidney as well. Schröder therefore conducted blood, to which carbonate of ammonia had been added, through the excised kidneys. The amount of urea in the blood remained the same, both before and after it had been passed through the kidneys. As the formation of urea from carbonate of ammonia is a process entirely analogous to that of the formation of hippuric acid from glycocol and benzoic acid, and as the excised kidney still brings about the latter synthesis, this experiment renders it extremely probable that carbonate of ammonia does not, in normal conditions, undergo conversion into urea in the kidneys.

Urea is therefore not formed in the kidneys but merely excreted by them. But where is it formed? As the muscles constitute 40 per cent. of the whole weight of the body, it was natural to think of them first. The compound, which forms

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[1] W. von Schröder, *Arch. f. exper. Path. u. Pharm.*, vol. xv. p. 364: 1882; and vol. xix. p. 373: 1885.

[2] The admirable care with which the methods of determining the urea were controlled and carried out renders Schröder's researches so valuable, and raises them far above those of his predecessors. In the decisive experiments the urea was weighed in pure crystals, which were subsequently analyzed to test their purity. The method is described *loc. cit.*, pp. 367–377.

[3] The results of previous work are in harmony with this, especially those of Prévost and Dumas in the *Ann. de Chim. et de Phys.*, vol. xxiii. p. 90: 1823. An account of the earlier literature is given by Voit, *Zeitschr. f. Biolog.*, vol. iv. p. 116, *et seq.:* 1868; and by Schröder, *loc. cit.*, pp. 364, 365.

the bulk of the nitrogenous end-products, might arise in the muscles. Schröder therefore conducted blood impregnated with carbonate of ammonia through the hind quarters of a dog which had been bled to death. The blood was introduced into the abdominal aorta below the renal arteries, and flowed out of the inferior vena cava. In one of the experiments 1100 c.cms. of blood were passed repeatedly through the limbs, so that the total flow during $4\frac{3}{4}$ hours amounted to 40 liters. "During the first four hours the limbs moved spontaneously, obviously from the stimulation to the spinal cord; its irritability continued to the end of the experiment. If one electrode was inserted into the spinal cord and the other applied to the leg, tetanus ensued. A part of the spinal cord evidently preserved its vitality, for stimulation of one leg produced contraction of the other." But the amount of urea in the blood was exactly the same before and after the passage of the blood. The conclusion therefore is that no urea is formed from carbonate of ammonia in the muscles and tissues of the body; unless indeed the objection were raised that the extremities could not be regarded as being under normal conditions in spite of the remarkable way they appeared to retain their vital properties.

The liver was the next organ to be thought of. It was to be expected that large quantities of urea could be formed only in a large organ. There are various reasons for believing that extensive metabolic processes go on in the liver, the largest of the glands. Schröder therefore conducted blood containing carbonate or formate of ammonia through the liver. The organ was removed from a small dog, whose blood was mixed with that of a large dog. The blood was introduced into the portal vein, and flowed out of the vena cava above the diaphragm. The hepatic artery was closed. After the blood had been allowed to pass for from four to five hours, the urea was found to amount to between double and treble the previous quantity. If blood without any carbonate of ammonia was conducted through the liver, the amount of urea increased but little, and then only in those experiments in which the liver and the blood were taken from dogs during digestion. If the blood and liver were removed from fasting dogs, and carbonate of ammonia was not mixed with the blood, no urea was formed; but this occurred directly carbonate of ammonia was added.

These results of Schröder's have been confirmed by Salomon,[1] who made his experiments on herbivora (sheep) as well as on dogs.

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[1] W. Salomon, Virchow's *Arch.*, vol. xcvii. p. 149: 1884.

Hence it follows that the synthesis of carbonate of ammonia into urea takes place in the liver.

Even this knowledge however does not advance our acquaintance with the precursors of urea. The antecedents of the small amount of urea, obtained by passing through the liver blood which had been taken from dogs during digestion, are still unknown. In all the other experiments the precursor (carbonate of ammonia) was artificially introduced. What justification is there for the conclusion that carbonate of ammonia is also normally the precursor of urea?

Schröder based his views on this subject upon pathological facts. If normally urea really arises in the liver from carbonate of ammonia, we should expect that in diseases of the liver the formation of urea would be arrested, and that a portion of the precursors would pass unchanged into the urine. We should especially anticipate this in cirrhosis of the liver, when the specific hepatic cells are pressed upon by the encroaching connective tissue, become atrophied, and in great part disappear.

The above assumption has been confirmed by observation. Investigators have found that in interstitial hepatitis the elimination of ammonia is increased both absolutely and relatively in proportion to the excretion of urea.[1] Healthy people excrete from 0.4 to 0.9 grm. of ammonia in twenty-four hours, and in cases of cirrhosis it rises to 2.5 grms.

It is thus rendered probable that part of the urea does arise normally from carbonate of ammonia, but the actual quantity is not yet known. It may be that only the small amount of ammonia produced by bacterial putrefaction in the intestines is absorbed by the blood of the portal vein to undergo this conversion in the liver into the innocuous urea. (Compare Lecture XXII.) Ammonia is a poison, and one of the functions of the liver is the prevention of ammonia intoxication. We must therefore acknowledge the possibility that the bulk of the urea takes its origin from another source.

The question as to the part played by the liver in the formation of urea might be definitely decided if we could succeed in keeping mammals alive for a considerable time after complete extirpation of the liver, or at any rate after cutting this organ out of the circulation. I have already mentioned (p. 284) the chief difficulty which prevents the carrying out of this operation, viz., the complete stasis which occurs in the

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[1] Hallervorden, *Arch. f. exper. Path. u. Pharm.*, vol. xii. p. 237: 1880; Stadelmann, *Deutsch. Arch. f. klin. Med.*, vol. xxxiii. p. 526: 1883.

veins of the abdominal viscera as a result of ligature of the portal vein. This difficulty has been overcome by establishing an artificial communication between the portal vein and the left renal vein or with the inferior vena cava.[1] The latter operation has been more especially carried out by V. Massen and J. Pawlow on dogs with such skill that several of the animals survived the operation for months. A complete exclusion of the liver from the circulation was not however effected, since the hepatic veins remained open, and since, even after ligature of the hepatic artery, blood could reach the liver by collateral anastomoses. In animals which had undergone this operation the ammonia of the urine was found to be increased to as much as 0.85 grm. in the twenty-four hours. The great bulk of the nitrogen, however, was still secreted as urea. In normal dogs the proportion of ammonia to urea was found to vary between $\frac{1}{22}$ and $\frac{1}{73}$; in the operated dogs between $\frac{1}{8}$ and $\frac{1}{33}$.[2]

Massen and Pawlow also attempted to extirpate the liver after establishing the venous fistula and tying the hepatic artery. As much as seven-eighths of the liver could be destroyed in this way, but the dogs never survived this operation more than six hours, and generally only two or three hours.

In our previous remarks on the precursors of urea no notice has been taken of a proteid product of decomposition which is very rich in nitrogen, *i. e.*, CREATIN. And yet creatin is important, as no other nitrogenous end-product of metabolism occurs in so large a quantity in the body. Only very small quantities of urea (of which from 30 to 40 grms. pass daily into the urine) are at all times found in the body. The total blood contains at most 2 grms., and it could not be detected in muscle. On the other hand, creatin, of which only from 0.5 to 2.5 grms. per diem pass as such or as creatinin into the urine, is found in the muscles alone to the extent of about 90 grms. This fact renders it probable that creatin is converted into urea and thus passes into the urine. This view has been held by many physiologists, but the following observation seemed opposed to it. It was found that creatin, introduced into an animal, reappears in the urine either unaltered or, consequent upon the

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[1] N. V. Eck, *Travaux de la Soc. des Naturalistes de St. Pétersbourg*, vol. x.: 1879. Bulletins de la Section Zoologique. Stolnikow, Pflüger's *Arch.*, vol. xxviii. p. 266: 1882; Stern, *Arch. f. Path. u. Pharm.*, vol. xix. p. 45: 1885; W. v. Schröder, *ibid.*, vol. xix. p. 373: 1885; Hahn, Massen, Nencki et Pawlow, *Arch. d. Sc. biol.*, vol. i. p. 401: St. Petersburg, 1892.

[2] Hahn and Nencki, *Arch. d. Sc. biol.*, vol. i. pp. 461–465: St. Petersburg, 1892.

loss of one molecule of water, as creatinin.[1] Hence it was inferred that creatin could not be one of the antecedents of urea. But this inference is incorrect; because the creatin introduced into the stomach or direct into the blood remains unaltered, it does not follow that the creatin formed in the muscles behaves in the same way. It is quite impossible for us artificially to introduce substances to the part where they would be decomposed in health. The muscular fibers withdraw from the blood nutritive substances only, and throw off the end products in an opposite direction. It is therefore even *à priori* unlikely that creatin, when artificially introduced, would enter the muscle and be decomposed. It must be noted that it is not only possible, but probable, that the large amount of creatin formed in muscle becomes further split up and, when converted into urea, given off to the blood. It is true that urea cannot be detected in muscle. Liebig, in his celebrated work on meat, says, "I think that I should be able to detect urea in meat-juice if only one-millionth part were present."[2] But it does not therefore follow that urea is not formed there. It is quite possible that it is formed in the muscle, but that it is immediately carried off into the blood-current.

I have already given the reasons for my view that the compounds into which the bulk of the nitrogen in the proteid molecule splits up are very poor in carbon. Creatin answers to this description; it contains only four atoms of carbon to three of nitrogen.

The composition of creatin has been thoroughly known since Volhard and Strecker succeeded in producing it synthetically. Volhard[3] heated an alkaline solution of sarcosin (methylglycocol) and cyanamid to 100° C. for a few hours in a closed vessel. On cooling, creatin crystallized out. Strecker went still more simply to work. If he allowed a saturated watery solution of sarcosin, with the requisite amount of cyanamid and a few drops of ammonia, to stand in the cold, a large quantity of creatin was obtained.[4]

The constitution of creatin may be more readily understood from a comparison of the composition of guanidin, which is

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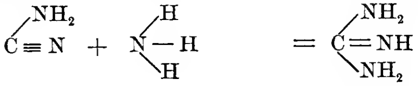
[1] G. Meissner, *Zeitschr. f. rat. Med.*, vol. xxiv. p. 100: 1865; vol. xxvi. p. 225: 1866; vol. xxxi. p. 283: 1868; C. Voit, *Zeitschr. f. Biolog.*, vol. iv. p. 111: 1868.

[2] Liebig, *Ann. d. Chem. u. Pharm.*, vol. lxii. p. 368: 1847.

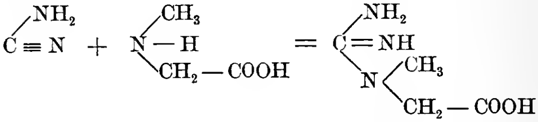
[3] Volhard, *Sitzungsber. d. Münch. Akad.*, vol. ii. p. 472: 1868; or *Zeitschr. f. Chem.*, p. 318: 1869.

[4] Strecker, *Jahresber. über Fortschr. d. Chem.*, note to p. 686: 1868. *Vide* also Horbaczewski, *Wien. med. Jahrb.*, p. 459: 1885.

quite analogous to creatin both in synthesis and in decomposition. Creatin is a substituted guanidin.



Cyanamid. Guanidin.



Cyanamid. Sarcosin. Creatin.

The analysis corresponds to the synthesis. On boiling with baryta water, the guanidin again splits into ammonia and cyanamid. But the cyanamid takes up one molecule of water and passes into urea. In the same way creatin breaks up into urea and sarcosin, a substituted ammonia. The close affinity of creatin to urea, and the possibility of its conversion into the latter, is thus amply proved.

Creatin is a neutral compound. By elimination of one molecule of water it passes into a strong base—creatin. This conversion is readily effected in an acid solution; creatin is as readily reformed by an alkaline solution. In conformity with this, the small amount of creatin daily excreted through the kidneys occurs chiefly as creatinin in acid urine, and as creatin in alkaline urine.[1]

Drechsel[2] has prepared a base homologous with creatin ($C_4H_7N_3O$) by the hydrolytic decomposition of various proteids, such as casein, conglutin, and gelatin. This body, which he called lysatin, has since been shown to be a mixture of lysin and arginin; and it is the latter body which belongs to the creatin group and like creatin yields urea on decomposition with baryta water.

As creatin breaks up into urea and methyl-amido-acetic acid, so arginin, on hydrolysis, yields urea and diamido-valerianic acid (ornithin). Drechsel reckons that $\frac{1}{9}$ of the total urea produced in our bodies by the decomposition of proteid may arise in this way by simple hydrolytic dissociation. We see therefore that some at any rate of the urea can be formed independently of the processes of oxidation and subsequent synthesis.

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[1] Voit, *Zeitschr. f. Biolog.*, vol. iv. p. 115: 1868.

[2] Drechsel, *Ber. d. deut. chem. Ges.*, vol. xxiii. p. 3096: 1890.

LECTURE XX

THE NITROGENOUS END-PRODUCTS OF METABOLISM (*continued*) —URIC ACID AND THE XANTHIN GROUP

Uric acid is the only nitrogenous end-product leaving the body in any quantity that remains for our discussion.

The amount of uric acid excreted in twenty-four hours varies greatly in the case of human beings. It depends upon the nature of the food. With a purely vegetable diet it amounts from 0.2 to 0.7 grm., and with a full meat diet it rises to 2 grms. and more. These differences cannot be explained merely by the varying amount of proteid in the food, for the proportion of uric acid to urea and to the total amount of nitrogen varies greatly. For instance, I found that the proportion of urea to uric acid in twenty-four hours in the urine of a healthy young man, when eating nothing but bread, $= \frac{20 \cdot 6}{0 \cdot 25} = 82$; and when living on meat, $= \frac{67 \cdot 2}{1 \cdot 4} = 48$. Uric acid is sometimes entirely absent from the urine of carnivorous animals, such as cats and dogs, and only a trace is generally found in the urine of herbivora. The bulk of the nitrogen however appears in this form in the urine of birds and reptiles.

Uric acid has the composition $C_5H_4N_4O_3$. One of the four hydrogen atoms is easily replaced by metals. If the uric acid be dissolved in a solution of sodium carbonate, the compound $C_5H_3NaN_4O_3$ is obtained. This compound is termed an acid urate. On dissolving in free alkalies, a second hydrogen atom is replaced by the alkaline metal. This compound is called a neutral urate. It is not known whether it occurs in the animal body.

Uric acid and all its 'acid salts' are with difficulty soluble in water. It is important, from a physiological and pathological point of view, to be accurately acquainted with its various degrees of solubility. It is well known that in disease, uric acid and urates may be precipitated from the fluids of the body, and become deposited in the joints and other organs and tissues, or from the urine in the tubules and pelvis of the kidney and in the bladder. The painful symptoms of what are known as the uric acid diathesis and of gout are due to this. It is therefore highly interesting to know under what conditions uric acid is soluble, and under what circumstances it is precipitated.

A gramme of free uric acid requires for its solution, at the temperature of the room, about 14 liters of water; at boiling heat, nearly 2 liters; and at the temperature of the body, from 7 to 8 liters.[1] The acid sodium urate dissolves in 1100 parts of cold and 124 of boiling water. The ammonia salt and the salts of the alkaline earths are much less soluble.

Sometimes as much as 2 grms. of uric acid are entirely dissolved in the normal urine, the volume of which in twenty-four hours ordinarily amounts to from 1500 to 2000 c.cms. It cannot be dissolved as a free acid, for, as we have just seen, 2 grms. of free uric acid require 15 liters of water at the temperature of the body, or ten times more than actually suffices for its solution. We must therefore assume that the uric acid is dissolved as an alkaline salt. But this is apparently opposed to the following fact: if clear acid urine be allowed to cool to the temperature of the room, the greater part of the uric acid usually separates out as a free acid in large and beautiful crystals, which are colored brown by the coloring matter brought down with it. The weight of the crystals obtained from the normal urine of twenty-four hours may amount to as much as 1 grm. How is this to be explained? If 2 liters of uric acid solution, saturated at the temperature of the body, be allowed to cool, only about 1 decigrm. of uric acid is precipitated. How then can it reach ten times that amount?

The explanation is as follows: If, at the temperature of the body, a saturated solution of acid urate of soda, with a neutral reaction, be mixed with a solution of acid phosphate of soda (NaH_2PO_4), with an acid reaction, the mixture will be acid. But if it be left to cool at the temperature of the room, the reaction becomes alkaline, and free uric acid crystallizes out. The mass-influence of the uric acid is diminished by cooling, because fewer of its molecules are dissolved in the unit of space. The mass-influence of the phosphoric acid becomes relatively stronger. This acid therefore takes possession of the sodium of the uric acid, and passes into the alkaline salt Na_2HPO_4. If the solution be heated afresh, the uric acid crystals redissolve, and the solution now gives an acid reaction. The uric acid in acid urine, which is always rich in phosphates of the alkalies,

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[1] As no account, so far as I know, has ever been given of the solubility of uric acid at the temperature of the body, I have made two determinations, varying between 35° and 40° C.: 1 grm. of uric acid required 7680 c.cms. of water in the first experiment, in the second 7320 c.cms., for solution.

behaves in exactly the same way. It can be proved that, on cooling the acid urine, the acidity decreases in proportion as the uric acid crystallizes out. When raised to the temperature of the body, the crystals redissolve.[1]

The phosphates of the alkalies thus play the same part in the solution of the uric acid that they do in the absorption of the carbonic acid in the blood and in the tissues (pp. 263–265).

It is doubtful whether the solution and elimination of the uric acid is to be thus explained in all cases. The acidity of the urine is occasionally found to be increased after the precipitation of uric acid.[2] It is possible that acids split off from neutral compounds by fermentation, or that dibasic arise from monobasic acids by decomposition. This process may at times be completed even within the urinary passages, the consequence being that uric acid is precipitated. We are as yet far from having obtained a satisfactory explanation of the manner in which the solution of uric acid is effected.

If the urine be only feebly acid or alkaline, as it is frequently with a vegetable or mixed diet, no free uric acid will be deposited on cooling; but if the urine be concentrated, acid urate of soda will be precipitated. This appears in exceedingly fine round granules which, like the free uric acid, are brown or red-brown, owing to the coloring matter brought down with them; this is found at the bottom of the vessel, and constitutes what is known as the lateritious deposit.

The uric acid sediment was formerly employed as a guide in diagnosing disease, but was very misleading. For instance, it was incorrectly assumed that an increase of sediment meant an increase of uric acid secretion. We have seen that the precipitation of uric acid depends not only on its absolute amount, but also on the concentration and acidity of the urine.[3] It appears however to depend on other conditions as well. It is often found that urines which deposit crystalline uric acid are neither richer in uric acid nor more concentrated; nor do they contain more free acid than others which remain clear or deposit urates.[4]

It is conceivable that uric acid circulates in the fluids of the body as a readily soluble compound with an organic substance, which appears in the urine, and is then split up

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[1] *Vide* Voit and Hofmann, "Ueber das Zustandekommen der Harnsäuresedimente," *Sitzungsber. d. bayr. Akad.*, vol. xi. p. 279: 1867. I have confirmed Voit and Hofmann's account by numerous experiments.

[2] Bartels, *Deutsch. Arch. f. klin. Med.*, vol. i. p. 24: 1866.

[3] Compare Botho Scheube, *Arch. f. Heilkunde*, vol. xvi. p. 185: 1876.

[4] Bartels, *loc. cit.*, p. 28.

by a fermentative process. If this happens in the organs or within the urinary passages, gouty concretions and vesical calculi are formed. At any rate, no increased formation of uric acid has hitherto been found in gout and in the uric acid diathesis. There is even less uric acid eliminated during an attack of gout.[1]

Besides, there is the important fact that a large amount of hydrochloric acid is necessary[2] in order to separate the uric acid from the urine for quantitative analysis, and that even then it separates very slowly and incompletely, and sometimes not at all, in spite of its being present in abundance.[3] This fact likewise argues that, at any rate, not all the uric acid is simply dissolved in the urine as a salt.

The chemical constitution of uric acid has been the subject of investigation by a large number of eminent chemists,[4] and its synthesis has been successfully accomplished.

Among the numerous modes of decomposition of uric acid, which have been accurately studied, the following is of peculiar physiological interest, because the products obtained play an important part in the animal economy.

Strecker[5] showed that uric acid, when heated with concentrated hydrochloric acid in a closed tube to 170° C., splits up, with hydration, into glycocol, carbonic acid, and ammonia:

$$C_5H_4N_4O_3 + 5H_2O = CH_2(NH_2)COOH + 3CO_2 + 3NH_3.$$

Strecker thought that uric acid would, while taking up only

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[1] Garrod, "The Nature and Treatment of Gout": London, 1859. An account of the literature on gout is given by Ebstein in his monograph, "Die Natur und Behandlung der Gicht": Wiesbaden, 1882.

[2] This phenomenon is probably to be explained by the formation of a soluble compound of the uric acid with urea. The uric acid can therefore only be precipitated when an amount of hydrochloric acid has been added equivalent to that of the urea. Compare G. Bunge, *Sitzungsb. d. Naturforsch. Gesell. z. Dorpat*, vol. vii., Appendix, p. 21: 1873; G. Rüdel, *Arch. f. exper. Path. u. Pharm.*, vol. xxx. p. 1: 1892.

[3] Salkowski, Pflüger's *Arch.*, vol. v. p. 210: 1872; Maly, *ibid.*, vol. vi. p. 201: 1872.

[4] Wöhler, Poggendorff's *Annal.*, vol. xv. p. 119: 1829; Liebig, *ibid.*, vol. xv. p. 569: 1829; and *Ann. d. Chem. u. Pharm.*, vol. v. p. 288: 1833; Wöhler and Liebig, *Ann. d. Chem. u. Pharm.*, vol. xxvi. p. 241: 1838; Adolf Baeyer, *ibid.*, vol. cxxvii. pp. 1, 199: 1863; Strecker, *ibid.*, vol. cxlvi. p. 142: 1868; and vol. clv. p. 177: 1870; Kolbe, *Ber. d. deutsch. chem. Ges.*, vol. iii. p. 183: 1870. Among the latest works on the constitution of uric acid may be mentioned L. Medicus, *Ann. d. Chem. u. Pharm.*, vol. clxxv. p. 230: 1875; Hill, *Ber. d. deutsch. chem. Ges.*, vol. ix. p. 370: 1876; and vol. xi. p. 1329: 1878; Horbaczewski, *Sitzungsber. d. Wien. Akad.*, vol. lxxxvi. p. 963: 1882; or *Monatshefte f. Chem.*, vol. iii. p. 796: 1882; and vol. vi. p. 356: 1885; and Emil Fischer, *Ber. d. deutsch. chem. Ges.*, vols. i., xvii. pp. 328, 1776: 1884.

[5] Strecker, Liebig's *Annal.*, vol. cxlvi. p. 142: 1868.

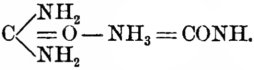
two molecules of water, break up first into glycocol and three molecules of cyanic acid:

$$C_5H_4N_4O_3 + 2H_2O = CH_2(NH_2)COOH + 3CONH.$$

It is well known that cyanic acid, on coming in contact with water, is at once converted into carbonic acid and ammonia. I may remind my readers that the watery solution of cyanate of potash effervesces with acids like a carbonate.

Strecker therefore regarded uric acid as a compound analogous to hippuric acid. As hippuric acid is a glycocol conjugated with benzoic acid, so uric acid is a glycocol conjugated with cyanic acid.

The synthesis of uric acid, which Horbaczewski[1] successfully accomplished in E. Ludwig's laboratory in Vienna, exactly corresponds to the decomposition observed by Strecker. Horbaczewski obtained uric acid by melting glycocol and urea together at from 200° to 230° C. It is well known that, on heating urea, ammonia volatilizes and cyanic acid is formed:—



$$C\left\langle\begin{matrix}NH_2\\ =O\\ NH_2\end{matrix}\right. - NH_3 = CONH.$$

Thus if urea be melted with glycocol, nascent cyanic acid is allowed to act on the glycocol; one decomposition product of the uric acid in a nascent state acts upon the other. This might *à priori* be expected to develop uric acid.

The following physiological fact observed by Wöhler appears to harmonize with these results of decomposition and synthesis. Wöhler[2] found uric acid, but no hippuric acid, in the urine of sucking calves, so long as they consumed nothing but milk. But as soon as they passed on to vegetable food, the uric acid disappeared, and hippuric acid was substituted.

It thus appears that the benzoic acid arising from vegetable diet seizes upon the glycocol and prevents the synthesis of uric acid.

If this interpretation be correct, we should expect, by the addition of aromatic compounds, to be able to prevent the formation of uric acid in human beings as well. This might even be of a therapeutic advantage in the treatment of gout. It is useless merely to give benzoate of sodium, as I have proved by many experiments. But here again it should not

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[1] Horbaczewski, *Sitzungsber. d. Wien. Akad.*, vol. lxxxvi. p. 963: 1882; or *Monatshefte f. Chem.*, vol. iii. p. 796: 1882; and vol. vi. p. 356: 1885.

[2] Wöhler, *Nachr. d. k. Ges. d. Wissensch. zu Göttingen*, vol. v. pp. 61–64: 1849.

be forgotten that it is not in our power to make the benzoic acid reach the proper point at the proper moment when the glycocol, before its union with the cyanic acid, could react with it. As already mentioned, the benzoic acid in vegetable food is not generally contained as such, but is formed in the body by the decomposition and oxidation of more complex combinations. It is quite possible that these latter are taken up by the cells in which glycocol occurs, while the benzoic acid already formed is rejected. At any rate, it must be remembered that to prevent the formation of uric acid in gout would only affect the symptoms. It is impossible to treat the essential cause of the disease, because it is quite unknown to us.

With a view to obtaining further insight into the constitution of uric acid, the products of its simultaneous decomposition and oxidation have been investigated—products obtained by the action of oxidizing agents. These products are likewise of great interest, because among them compounds occur which are also met with in the metabolism of the animal body.

A solution of permanganate of potash causes uric acid to break up, even in the cold, into allantoin and carbonic acid:[1] $C_5H_4N_4O_3 + O + H_2O = C_4H_6N_4O_3 + CO_2$.

Allantoin was discovered by Vauquelin[2] in the allantoic fluid of the cow, was subsequently found by Wöhler[3] in calves' urine as well, and was further investigated both by him and by Liebig.[4] Later this compound was also detected in the allantoic fluid and in the urine of new-born children, and occasionally in dogs' urine.[5]

The further action of oxidizing agents upon allantoin[6] produces urea and oxalic acid, and the latter ultimately, under the same influence, yields carbonic acid.

If nitric acid be employed for the purpose of splitting up and oxidizing uric acid, urea and carbonic acid are again obtained as end-products. Compounds occur as intermediary products which, although they do not appear in the animal

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[1] Claus, *Ber. d. deutsch. chem. Ges. d. Wissensch. zu Göttingen*, vol. v. pp. 61–64: 1849.

[2] Buniva et Vauquelin, *Ann. de Chim.*, vol. xxxiii. p. 269, ann. viii^e.: 1799. *Vide* also Lassaigne, *Ann. de Chim. et de Phys.*, vol. xvii. p. 301: 1821.

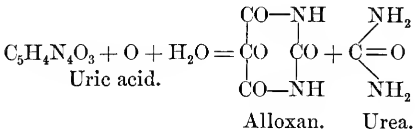
[3] Wöhler, *Nachr. d. k. Ges. d. Wissensch. zu Göttingen*, p. 61: 1849.

[4] Wöhler and Liebig, *Ann. d. Chem. u. Pharm.*, vol. xxvi. p. 244: 1838.

[5] E. Salkowski, *Ber. d. deutsch. chem. Ges.*, vol. ix. p. 719: 1876; and vol. xi. p. 500: 1878.

[6] For the synthesis and composition of allantoin, *vide* Grimaux, *Compt. rend.* vol. lxxxiii. p. 62: 1876.

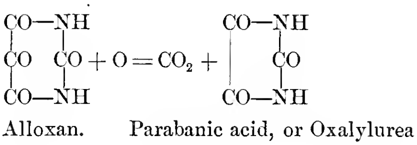
body, are of interest in so far as they help to throw some light upon the constitution of uric acid. Alloxan and urea are the first compounds formed by the nitric acid in the presence of cold:



$$C_5H_4N_4O_3 + O + H_2O = \begin{array}{l} CO-NH \\ CO \quad CO \\ CO-NH \end{array} + C{=}O\begin{array}{l} NH_2 \\ NH_2 \end{array}$$

Uric acid. Alloxan. Urea.

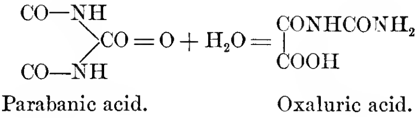
Alloxan, when heated with nitric acid, passes into parabanic and carbonic acids:



$$\begin{array}{l} CO-NH \\ CO \quad CO \\ CO-NH \end{array} + O = CO_2 + \begin{array}{l} CO-NH \\ \quad\;\; CO \\ CO-NH \end{array}$$

Alloxan. Parabanic acid, or Oxalylurea

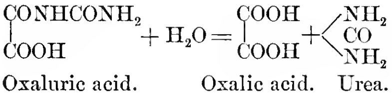
The parabanic acid, with hydration, passes into oxaluric acid:



$$\begin{array}{l} CO-NH \\ CO-NH \end{array}\!\!>CO = O + H_2O = \begin{array}{l} CONHCONH_2 \\ COOH \end{array}$$

Parabanic acid. Oxaluric acid.

The latter, by taking up a second molecule of water, breaks up into oxalic acid and urea:



$$\begin{array}{l} CONHCONH_2 \\ COOH \end{array} + H_2O = \begin{array}{l} COOH \\ COOH \end{array} + CO\begin{array}{l} NH_2 \\ NH_2 \end{array}$$

Oxaluric acid. Oxalic acid. Urea.

Oxaluric acid occurs in the human urine[1] in minute quantities.

The following formula, which was composed by Medicus[2] and confirmed by Emil Fischer[3] from extensive observations,

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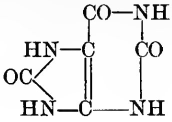
[1] Ed. Schunck, *Proceed. Roy. Soc.*, vol. xvi. p. 140: 1868; C. Neubauer, *Zeitschr. f. anal. Chem.*, vol. vii. p. 225: 1868.

[2] Medicus, *Ann. d. Chem. u. Pharm.*, vol. clxxv. p. 230: 1875.

[3] Fischer, *Ber. d. deutsch. chem. Ges.*, vol. xvii. pp. 328, 1776: 1884.

agrees with all the decompositions of uric acid we have described:



Another synthesis of uric acid,[1] also discovered by Horbaczewski, agrees well with this structural formula. He found it could be synthesized by fusing together trichlorlactic acid and urea.

As we have seen that uric acid is transmuted into urea and carbonic acid by oxidizing agents outside the organism, we should expect to find the same process going on within the organism, and that uric acid is one of the antecedents of urea. If uric acid be introduced into the organism of a dog, it certainly becomes almost entirely changed into urea.[2] But it by no means follows that part of the urea normally formed arises from uric acid. This idea is frequently met with, and especially in pathological literature. It was thought that, in disturbances of external and internal respiration (such as affections of the lungs, anemia, etc.), an increase takes place in the elimination of uric acid as a product of incomplete combustion. This supposition has not, however, been confirmed. Senator[3] could detect no increase in the excretion of uric acid in dogs, cats, and rabbits when respiratory disturbances were artificially induced; nor could Naunyn and Riess[4] do so after venesections. Moreover the numerous accounts given of the increased elimination of uric acid in human beings in consequence of respiratory disturbances, do not rest on exact observation. In the first place, investigators fell into the error, already alluded to, of inferring an increase of uric acid from an increase of sediment; and in the second place, they did not sufficiently take into consideration how much the formation of uric acid depends upon diet. It should be especially noted that a fasting, and particularly a febrile person—in whom it is well known that the pro-

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[1] J. Horbaczewski, *Monatshefte für Chemie*, vol. viii. pp. 201, 584: 1887.

[2] Zabelin, Liebig's *Annal. d. Chem. u. Pharm.*, Suppl., vol. ii. p. 326: 1862 and 1863. The views of earlier authors on the conversion of uric acid into urea will be found here. [It has been shown recently by Minkowski that a considerable amount of the uric acid is converted in the organism of the dog into allantoin, in which form it is excreted in the urine. Minkowski, *Arch. f. exper. Path. u. Pharm.*, vol. xli. p. 375: 1898.]

[3] Senator, Virchow's *Arch.*, vol. xlii. p. 35: 1868.

[4] B. Naunyn and L. Riess, Du Bois' *Arch.*, p. 381: 1869.

teid-decomposition is increased—behaves exactly like a person who lives on meat. The results of all calculations bearing upon the elimination of uric acid in respiratory disturbances, and concerning the relation of uric acid to urea in these affections, vary within the same limits as they do in the case of healthy people.

Increased excretion of uric acid has hitherto been proved only in the case of one disease, leukemia. Bartels[1] recounts that he found 4.2 grms. of uric acid in the urine of a leukemic patient during twenty-four hours, of which 1.8 grm. had crystallized out. O. Schultzen[2] even found, in the urine of a case of leukemia during twenty-four hours, a sediment consisting of 4.5 grms. of free uric acid and 1.45 grm. of urate of ammonia. Such large amounts have never been observed in healthy people. In the cases of leukemia where the amount of uric acid does not exceed that of healthy people, the proportion of uric acid to urea is increased, frequently in the proportion of only 12 grms. of the latter to 1 grm. of uric acid.[3] Fleischer and Penzoldt[4] have made a careful investigation on this subject. They dieted a leukemic patient and a person in good health in precisely the same way; they both excreted the same amount of urea, but the leukemic patient eliminated daily an average of 1.29 grm. of uric acid, while that eliminated by the healthy person amounted to 0.66 grm., or half as much. Careful experiments carried out by Stadthagen[5] in Kossel's laboratory led to similar results.

This occurrence cannot, for the reasons already given, be referred to a diminution of oxygen in consequence of the decrease in red blood-corpuscles. It was therefore thought that the cause was to be sought in the enlargement of the spleen and in the increase of leucocytes. Uric acid is constantly found in the spleen, which has given rise to the idea that it is chiefly formed here. Enlargement of the spleen, however, occurs in other diseases, in intermittent fever and in typhoid, without any increase of uric acid that could be detected.[6] Nor could Stadthagen confirm the view that uric acid occurred in the spleen; he could not detect even a trace of it in the liver

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[1] Bartel's *Deutsch. Arch. f. klin. Med.*, vol. i. p. 23: 1866.

[2] Steinberg, "Uber Leukämie," Inaug. Dissert.: Berlin, 1868.

[3] H. Ranke, "Beobachtungen und Versuche über die Ausscheidung der Harnsäure," p. 27: München, 1858; and Salkowski, Virchow's *Arch.*, vol. l. p. 174: 1870; and vol. lii. p. 58: 1871.

[4] Fleischer and Penzoldt, *Deutsch. Arch. f. klin. Med.*, vol. xxvi. p. 368: 1880.

[5] Stadthagen, Virchow's *Arch.*, vol. cix. p. 396: 1887.

[6] Bartels, *Deutsch. Arch. f. klin. Med.*, vol. i. p. 28: 1866.

and spleen of either a leukemic patient or a healthy person. It is possible that uric acid may be a product of the metabolism of leucocytes, independent organisms which travel through our tissues, after the manner of 'symbionta.' Uric acid has been observed to be the end-product of tissue-change in all kinds of the lower animals. In this connection it is noteworthy that quinine, which diminishes the ameboid movements of leucocytes, also lessens the elimination of uric acid.[1]

Horbaczewski[2] confirms Stadthagen's statement that the spleen contains no uric acid. In the fresh splenic pulp of calves directly after death he could detect no, or only the slightest trace of, uric acid. If, however, the fresh splenic pulp were allowed to stand with blood at the temperature of the body, considerable quantities of uric acid were formed,[3] *e. g.*, .14 grm. from 100 grms. of splenic pulp in seven and a half hours. This formation of uric acid also occurred if, instead of splenic pulp, an extract obtained by boiling the spleen with normal salt solution were used, and allowed to stand some hours with blood at the body temperature. In this process oxygen is necessary, since only small quantities of uric acid are formed, if hydrogen be led through the mixture of splenic pulp and blood. If the splenic pulp be allowed to putrefy with water at 50° C., xanthin and hypoxanthin can be prepared from the watery extract. These bases however, like the uric acid, could not be found by Horbaczewski pre-formed in the splenic pulp. Moreover they are not the precursors of uric acid since, as is well known, they are not converted by oxidation into uric acid. We must assume that the xanthin bases and the uric acid are formed according to the varying conditions under which the experiment is carried out, from some common precursor. This precursor is a substance derived from some nuclein compound of the nuclei of the leucocytes, and probably occurs in all other tissues which contain nuclein.

The theory that uric acid is the result of imperfect respiration is negatived by the simple fact that in birds, which of all animals have the most active respiration, the bulk of the nitrogen leaves the body as uric acid. The nitrogen may be introduced into the organism of the bird in whatever form you

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[1] Ranke, *loc. cit.* This account has been amply confirmed, especially by Prior's thorough investigation, Pflüger's *Arch.*, vol. xxxiv. p. 237: 1884. The whole literature will be found here.

[2] J. Horbaczewski, *Sitzungsb. d. Akad. d. Wissensch. in Wien.*, Math.-nat. Kl., vol. xcviii. pt. iii., July, 1889, and vol. c. pt. iii., April, 1891.

[3] These results have been confirmed by P. Giacosa, *Wien. med. Blätter*, No. 32: 1890.

like—as an amido-acid: leucin, glycocol, or aspartic acid;[1] as urea;[2] as carbonate or formate of ammonia;[3] as hypoxanthin[4]—it invariably appears in the urine as uric acid.

We cannot even guess in what way these nitrogenous compounds take part in the synthesis of uric acid. For instance, carbonate of ammonia alone cannot furnish material for the formation of uric acid; a further compound, rich in carbon, and containing little or no nitrogen, is required. Either glycocol or lactic acid would satisfy these requirements, but nothing definite is known on this point.

It now only remains for us to consider where the uric acid is formed. This is important from a physiological as well as from a pathological point of view. The most complete investigations upon this subject of recent times have been made by Schröder[5] and Minkowski.[6]

Schröder succeeded, in Ludwig's laboratory, in overcoming the immense difficulties encountered in the extirpation of the kidneys of birds. Hens lived from five to ten hours after their kidneys had been either extirpated or detached from the circulation by ligaturing the aorta and vena cava above the kidney. In this time uric acid had accumulated in the organs. A considerable amount of uric acid was obtained from the heart and the lungs together with the blood in them, but none from the normal organs, by the method adopted by Schröder. Hence it follows that the uric acid is not produced, or at any rate not exclusively formed, in the kidneys of fowls. Experiments in which snakes' kidneys were extirpated gave the same results, only that here the amount of uric acid that accumulated was larger, because snakes survive the operation for a much longer time. They lived from five to nine days afterwards, and after death a large quantity of uric acid was found in all their organs, but most abundantly in the spleen. A considerable amount of uric acid was obtained from the blood. Hence also in snakes uric acid is not primarily formed in the kidneys.

The locality of the formation of uric acid in mammals has not been experimentally investigated. At the same time, the existence of small amounts of uric acid in the liver, lungs, and

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[1] Von Knieriem, *Zeitschr. f. Biolog.*, vol. xiii. p. 36: 1877.

[2] Meyer and Jaffé, *Ber. d. deutsch. chem. Ges.*, vol. x. p. 1930: 1877. *Vide* also Cech, *ibid.*, vol. x. p. 1461: 1877.

[3] Von Schröder, *Zeitschr. f. physiol. Chem.*, vol. ii. p. 228: 1878.

[4] W. von Mach, *Arch. f. exper. Path. u. Pharm.*, vol. xxiv. p. 389: 1888.

[5] Von Schröder, Du Bois' *Arch.*, Sup., p. 113: 1880; and "Beiträge zu Physiol., Carl Ludwig zu seinem 70 Geburtstage gewidmet von seinen Schülern," p. 89: Leipzig, 1887.

[6] Minkowski, *Arch. f. exper. Path. u. Pharm.*, vol. xxi. p. 41: 1886.

other organs has been ascertained.[1] The occurrence in gout or large quantities of uric acid in the joints, tendons, and ligaments, under the skin, and in other organs, without any previous disturbance in the functions of the kidney, seems to show that uric acid is not primarily formed in the kidneys in the case of mammals any more than it is in the case of birds and reptiles.

Minkowski[2] endeavored to ascertain whether this process went on in the liver. He carried out his experiments on birds. The difficulties met with in mammals, in endeavoring to cut the liver out of the circulation, do not occur in birds, and there is no need in the latter to guard against the intense congestion in the portal system by establishing artificial communication. Fortunately, such a communication has a natural existence in birds. Birds have a vascular system in the kidney similar to the portal circulation in the liver. There is a vena advehens in the kidney which brings to that organ the blood of the caudal vein, the iliac veins, and the veins leading from the pelvic organs. This vena advehens communicates with the portal veins by means of Jacobson's vein. After tying the portal vein therefore, the blood from the intestine can pass through the kidneys to the inferior vena cava, and no stagnation occurs.[3] Minkowski therefore tried, by experiments on birds, to find out what influence the removal of the liver has upon the composition of urine. He made his experiments on geese, because these large birds yield a sufficient amount of urine for the purpose of analysis, and because they secrete urine in abundance after removal of the liver. He operated upon as many as sixty geese, and in most cases, not only tied the hepatic vessels, but also completely extirpated the liver, except a very small remnant which he was obliged to leave in the immediate neighborhood of the vena cava, as in birds this latter passes through the liver. This remnant was destroyed by crushing. The animals thus operated upon mostly lived for more than six hours, and a few of them for twenty hours. The large intestine was tied above the cloaca in order to obtain the urine in a pure condition.

The result obtained was that the total nitrogen eliminated after the extirpation of the liver was not greatly diminished; it amounted to about from one-half to two-thirds of the

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[1] An account of the literature is given by Schröder, Du Bois' *Arch.*, Sup., p. 143. For the opposite view of Stadthagen, see the earlier reference.

[2] Minkowski, *loc. cit.*, and *Arch. f. exper. Path. u. Pharm.*, vol. xxxi. p. 214: 1893.

[3] Stern, *Arch. f. exper. Path. u. Pharm.*, vol. xix. p. 45: 1885.

quantity normally excreted by geese in the same time. On the other hand, the proportion of uric acid to the total nitrogen in the urine was very different. In healthy geese the nitrogen eliminated as uric acid amounts to from 60 to 70 per cent. of the total nitrogen; in geese after removal of the liver, only to from 3 to 6 per cent.

The relative amount of another nitrogenous constituent of the urine, ammonia, is altered in the reverse direction after extirpation of the liver. The ammonia in the urine of normal geese amounts to from 9 to 18 per cent. of the total nitrogen; that in the urine of geese after extirpation of the liver, from 50 to 60 per cent.

From this Minkowski concludes that ammonia is a normal antecedent of uric acid, and that the synthetic conversion of ammonia into uric acid in the organism of birds can only take place if the liver is free to perform its functions. Minkowski does not say that the liver is the locality of uric acid formation. It is possible that the functions of the liver are only indirectly called into play in the formation of uric acid in other organs.

The following very important fact observed by Minkowski may be interpreted in this sense. A very large quantity of lactic acid was found in the urine of geese after removal of the liver. Minkowski could not detect any lactic acid in the normal urine of geese, whereas after the operation there was so large a quantity as to be equivalent to the amount of ammonia excreted, and sufficient to make the urine strongly acid.

The extirpation of the liver is, therefore, in some way as yet inexplicable, followed by the appearance of large quantities of lactic acid, and the formation of uric acid being inhibited in any organ is perhaps only indirectly the consequence of the occurrence of the acid. We have already seen that acids check the formation of urea and increase the elimination of ammonia in the organism of mammals. Why may not acids have the same inhibitory effect upon the formation of uric acid in the organism of birds? In fact, by administering sodium carbonate, Minkowski succeeded in reducing the elimination of ammonia in a normal goose from 11 to 3 per cent. of the total nitrogen.

I will only add that in diseases of the liver, and especially in acute atrophy of the liver, and in cases of phosphorus poisoning, large quantities of lactic acid have been observed in the urine.[1] May not the increased elimination of ammonia in cirrhosis of the liver (p. 295) be likewise referred to this

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[1] Schultzen and Riess, *Ann. des Charité-Krankenhauses*, vol. xv.: 1869.

fact? So far as my knowledge extends, no determinations have ever been made of the acidity of, and the lactic acid present in, the urine of persons suffering from cirrhosis of the liver.

I will also take this opportunity of mentioning that the occurrence of an organic acid (oxybutyric acid) and simultaneously an increased elimination of ammonia has also been observed in cases of diabetes mellitus.[1]

It may even be doubted whether ammonia is the normal antecedent of urea and of uric acid. It is possible that the nitrogen, which under normal circumstances splits off from the proteid molecule as a neutral compound, separates as ammonia under the influence of the abnormal acids.

The facts observed by Minkowski may therefore be interpreted in many different ways. Minkowski himself inclines to the idea that the bulk of the uric acid in the liver is normally formed by synthesis from ammonia and a non-nitrogenous substance, and imagines this latter to be lactic acid.[2] Minkowski grounds this view on the probability of ammonia and lactic acid both having a common source in proteid. As already stated, he always found the lactic acid in quantities equivalent to the ammonia. It increased in quantity with the amount of proteid in the food, and was independent of the addition of carbohydrates; it increased also under the same condition under which an increase of uric acid normally takes place.

Of the numerous facts ascertained by Minkowski, I would emphasize the following:

Besides the uric acid and the ammonia, which form the bulk of the nitrogenous compounds in the normal urine of

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[1] Hallervorden, *Arch. f. exper. Path. u. Pharm.*, vol. xii. p. 268: 1880; Stadelmann, *ibid.*, vol. xvii. p. 419: 1883; Minkowski, *ibid.*, vol. xviii. pp. 35, 147: 1884; Külz, *Zeitschr. f. Biolog.*, vol. xx. p. 165: 1884; H. Wolpe, *Arch. f. exper. Path. u. Pharm.*, vol. xxi. p. 138: 1886.

[2] The lactic acid found by Minkowski in the urine of geese whose livers had been removed was the optically active sarcolactic acid. There are known to be three isomeric lactic acids: ethylene lactic acid [$CH_2(OH)CH_2COOH$] or hydracrylic acid, which has not been detected in the animal body, and the two ethylidene lactic acids [$CH_3CH(OH)COOH$]. Of the two last, the lactic acid of fermentation, which is formed by the fermentation of sugar of milk in milk, and by the fermentation of the carbohydrates in the intestine, is optically inactive; the other, the sarcolactic acid, is optically active, as it rotates the plane of polarization to the right. The latter is obtained from muscles (compare Lecture XXIII.), and is met with frequently in pathological products: in urine, in phosphorus-poisoning and atrophy of the liver, in osteomalacia, in the sweat in puerperal fever, and in various pathological exudations. We owe the most minute inquiries into isomeric lactic acids to J. Wislicenus (*Ann. d. Chem. u. Pharm.*, vol. clxvi. p. 3: 1873; and vol. clxvii. pp. 302, 346: 1873), and to E. Erlenmeyer (*ibid.*, vol. clviii. p. 262: 1871; and vol. cxci. p. 261: 1878). A summary of the literature on isomeric lactic acids is given in these works.

birds, there is always a small amount of urea. The nitrogen eliminated in this form amounts to from about 2 to 4 per cent. of the total nitrogen. The proportion of urea to the total nitrogen remained unaltered after extirpation of the liver. The urea in the urine of birds is therefore not formed in the liver. But of course this does not justify any conclusion with regard to the locality of the formation of urea in mammals.

If urea be artificially introduced into the organism of normal birds, the nitrogen of the urea, according to the experiments of Meyer and Jaffé already quoted, reappears as uric acid in the urine. Minkowski injected solutions of urea either subcutaneously or into the stomach of his geese, after removal of the liver; the urea reappeared in the urine unaltered. This fact also seems to warrant the conclusion that uric acid is formed by synthesis in the liver, but it is capable of being otherwise interpreted. I may express the hope that the artificial transmission of blood through the excised liver of birds may soon give a satisfactory reply to this question.

The facts obtained both by Meissner[1] and by Schröder[2] agree in showing that the amount of normal uric acid is always larger in the liver than in the blood of birds; and they are moreover in harmony with the theory that uric acid, or at any rate a portion of it, is formed in the liver of birds.

These experiments on birds do not permit of any conclusion being drawn as to the seat of formation of uric acid in mammals, and there are no grounds for assuming that the chief part of the uric acid in mammals is also formed in the liver. The fact that the excretion of uric acid is unaltered in cirrhosis of the liver is against such a view.

In all the tissues of our body, and especially in the nuclei of the cells, there are small quantities of two bases rich in nitrogen, the empirical formulæ of which would lead to the conclusion that they are closely related genetically to uric acid. I mean XANTHIN and HYPOXANTHIN, or sarcin.[3] They differ from uric acid only in their smaller amount of oxygen:

Uric acid	$C_5H_4N_4O_3$
Xanthin	$C_5H_4N_4O_2$
Hypoxanthin	$C_5H_4N_4O$

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[1] Meissner, *Zeitschr. f. rat. Med.*, vol. xxxi. p. 144: 1868.

[2] W. von Schröder, "Beiträge zur Physiol., Carl Ludwig zu seinem 70 Geburtstage gewidmet von seinen Schülern," p. 98, Leipzig: 1887.

[3] J. Piccard, *Ber. d. deutsch. chem. Ges.*, vol. vii. pp. 1714–1719: 1874; Kossel, *Zeitschr. f. physiol. Chem.*, vol. vi. p. 422: 1882; vol. vii. p. 7: 1882.

As yet however no one has succeeded in transmuting the three compounds into one another.[1] The facts that xanthin on oxidation yields alloxan and, when acted on by fuming hydrochloric acid, glycocol, seem to point to its having a constitution somewhat analogous to that of uric acid.[2]

But there is, in close affinity to xanthin, a third compound, GUANIN[3] ($C_5H_5N_5O$), which frequently occurs in the tissues together with xanthin and hypoxanthin, and, like these, is a decomposition-product of the nuclein of the cell-nuclei. This is converted into xanthin by the action of nitrous acid.

More recently Kossel[4] has discovered a fourth base rich in nitrogen as a constituent of the nuclei; this he terms ADENIN. It has the composition $C_5H_5N_5$ and is therefore a polymer of hydrocyanic acid, and is related to hypoxanthin in the same way as guanin is to xanthin. It is converted into hypoxanthin by nitrous acid.

Only a very small quantity of xanthin is invariably present in human urine;[5] in rare cases it may form vesical calculi.

Xanthin, hypoxanthin, guanin, and adenin, which are usually designated by the generic name of xanthin bases, undoubtedly belong to the antecedents of urea or of uric acid.[6] They occur in too large a quantity in the tissues, and in too small a one in the urine, for it to be possible that they are eliminated unchanged. Guanin is, like creatin, a substituted guanidin. All the reasons which were adduced in favor of the conversion of creatin into urea are equally applicable to guanin.

The xanthin bases are however not merely end-products: they are also initial products of metabolism, since they form important constituents of the heads of spermatozoa. The chemical constitution of these bases acquires therefore considerable physiological interest. Even if we are unable at present

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[1] Emil Fischer (*Ber. d. deutsch. chem. Ges.*, vol. xvii. pp. 328, 329: 1884) was unable to confirm Strecker's account that uric acid could be reduced to xanthin and hypoxanthin by nascent hydrogen, and that hypoxanthin could be oxidized into xanthin by nitric acid. *Vide* also Kossel, *Zeitschr. f. physiol. Chem.*, vol. vi. p. 428: 1882.

[2] For the composition of xanthin, see Emil Fischer, *Ann. d. Chem. u. Pharm.*, vol. ccxv. p. 253: 1882; *Ber. d. deutsch. chem. Ges.*, vol. xv. p. 453: 1882; and Arm. Gautier, *Compt. rend.*, vol. xcviii. p. 1523: 1884 (Synthesis of xanthin).

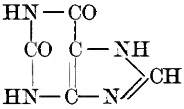
[3] J. Piccard, *loc. cit.;* Kossel, *Zeitschr. f. physiol. Chem.*, vol. vii. p. 16: 1882; vol. viii. p. 404: 1884.

[4] Kossel, *ibid.*, vol. x. p. 250: 1886.

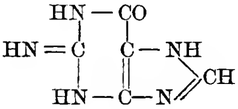
[5] Neubauer, *Zeitschr. f. analyt. Chem.*, vol. vii. p. 225: 1868.

[6] *Vide* Stadthagen, Virchow's *Arch.*, vol. cix. p. 390: 1887. An account of the literature on the xanthin bodies, and the part they play in the formation of uric acid, is given here.

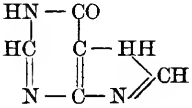
to say anything concerning their function, we must expect that the knowledge of their properties will in the near future open up a whole series of important questions. According to the most recent researches of Emil Fischer, the constitution of the xanthin bases may be represented as follows:



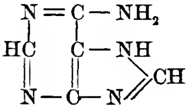
Xanthin.



Guanin.



Hypoxanthin.



Adenin.

LECTURE XXI

THE FUNCTIONS OF THE KIDNEYS, AND THE COMPOSITION OF THE URINE

In the last lecture we became acquainted with the end-products in which the bulk of the nitrogen leaves the body through the kidneys. The elimination of the nitrogenous end-products of metabolism is not, however, the sole function of the kidneys. To the kidneys is assigned the duty of maintaining the composition of the blood invariable, of rejecting from the blood everything that does not belong to it normally, whether an abnormal constituent or a normal one that has increased beyond its normal amount.

This function is usually ascribed to the epithelial cells of the renal tubules, although it appears to me that it might with equal justice be referred to the cells of the capillary wall. There is no reason for assuming that the capillary wall plays a passive part in the process of secretion. We know that it consists of cells joined together like mosaic work, and that each of these cells is a living unit, an organism by itself, to which we are *à priori* justified in ascribing as complex functions as to the epithelial cells of the tubules.

The cells of the capillary wall and those of the epithelium perform the work of rejecting the substances which do not normally form part of the composition of the blood, and this they do without regard to the laws of diffusion and endosmosis or to the conditions of solubility. They eliminate everything useless or superfluous — crystalloid and colloid substances, both soluble and insoluble, both alkaline and acid.

Sugar and urea are both easily soluble in water and readily diffusible; they are both always circulating with the blood through the renal capillaries. Sugar, which is an important food-stuff, is retained; urea, which is an end-product, is excreted. The purpose is manifest, though we are unable to explain the reason. It does not at present admit of a mechanical explanation. If the sugar exceed the normal quantity, it is secreted.

Proteids form the main constituents of blood-plasma; but they are never allowed to pass by a healthy epithelium. The normal proteids of the plasma appear in the urine only when the renal epithelium has undergone pathological alteration, or has been impaired by impeded circulation of the blood and by an arrest of the supply of oxygen.[1] But the normal proteids of the plasma cannot pass the normal and well-nourished epithelium; and this not by reason of their colloid nature, for as soon as a proteid that does not belong to the normal constituents of the plasma, such as egg-albumin or a solution of casein, is allowed to enter the blood, it reappears in the urine.[2] This applies not only to colloid substances, but also to such as are absolutely insoluble and immiscible with water, which are removed by the activity of the cells into the commencement of the renal tubules, if they do not belong to the normal constituents of the blood. Among these we may mention foreign fatty matters (cod-liver oil), superfluous cholesterin, resins, and the like.

If the blood becomes too alkaline, as it may by conversion of vegetable salts of alkalies into carbonates, the renal cells separate the excess of these carbonates from the blood. If the alkalescence of the blood be diminished—perhaps by the liberation of sulphuric acid and phosphoric acid, caused by the decomposition of proteids of nucleins and lecithins—the renal cells take up the neutral salts of the blood, separate them into acid and alkaline, convey the acid salts into the urine, and the alkaline back into the blood, until the normal alkalinity is restored.

The epithelial cells are of very varying form and size in different parts of the urinary tubules. This renders it probable that different portions have different functions to perform; that only certain constituents of the urine are eliminated by

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[1] Heidenhain in Hermann's "Handbuch der Physiol.," vol. v. pt. i. pp. 337, 371: Leipzig, 1883.

[2] J. Forster, *Zeitschr. f. Biolog.*, vol. xi. p. 526: 1875. In this paper the earlier views of Bernard, Lehmann, Stokvis, and Creile are mentioned. See further R. Neumeister, "Zur Frage nach dem Schicksal der Eiweissnährung im Organismus," *Sitzungsber. d. phys. med. Ges. z. Würzburg:* 1889. Albuminuria occurs as a symptom of so many and various diseases, and can be caused in so many different ways that a discussion of the subject is best left to the pathologist. At present chemistry can contribute little to the explanation of albuminuria or of its relation to the other symptoms of the diseases in which it occurs. A connected account of our present knowledge of the subject has been given by H. Senator, "Die Albuminurie in physiologischer u. klinischer Beziehung u. ihre Behandlung," 2d ed., Berlin: 1890. For the methods of detection of proteid in urine, I would refer the reader to the well-known "Handbuch d. physiologisch- u. pathologisch-chemischen Analyse" by Hoppe-Seyler.

one part, and different ones by another. It is known as a fact that the coloring matter, carmine, when it gets into the blood, is excreted by the Malpighian bodies,[1] whereas indigo[2] and bile pigments[3] are excreted by the convoluted tubules and Henle's loops. In birds, uric acid is found only in the epithelium of the convoluted tubules, never in other parts.[4] The purpose of this arrangement is evident: were the uric acid to be excreted by the Malpighian bodies, it might remain there and form concretions; whereas the crystals eliminated by the convoluted tubules are being constantly washed down by the fluid secreted by the glomeruli.

The structure of the glomeruli is very puzzling, and is seen in no other gland. The widening of the arteries into the capillary system, and their reunion to form an efferent vessel, which is narrower than the afferent one, appear to be arranged for the purpose of slowing the blood and of increasing the pressure. But we are at present incapable of even suggesting a theory as to what significance this precaution has in the formation of urine, and as to what constituents are formed or eliminated in the glomeruli. It has not been found that blood-pressure has any influence in any part of the body upon the quantity and quality of the transudation formed.[5]

It has hitherto not been proved that the nervous system exercises any direct influence upon the epithelial cells of the kidney, as it has been ascertained to exercise in the case of the salivary glands, and as is also probable in the case of the remaining glands of the digestive apparatus. The renal nerves appear only to act upon the vessels. This difference might *à priori* have been expected. The digestive glands form their secretion from the normal constituents of the blood. The impulse to greater activity of the epithelial cells cannot therefore proceed from the blood, but from the alimentary canal, where the need of more secretion makes itself felt; this necessitates the intervention of nerves. The kidneys behave differently; for the impulse to increased activity of the renal cells must proceed from the abnormally increased constituents

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[1] Chrzonsczewski, Virchow's *Arch.*, vol. xxxi. p. 189: 1864; Wittich, *Arch. f. mikrosk. Anat.*, vol. xi. p. 77: 1875.

[2] Heidenhain, *ibid.*, vol. x. p. 30: 1874; Pflüger's *Arch.*, vol. ix. p. 1: 1875.

[3] Möbius, *Arch. f. Heilk.*, vol. xviii. p. 84: 1877.

[4] Wittich, Virchow's *Arch.*, vol. x. p. 325: 1856; Zalesky, "Unt über den urämischen Process und die Function der Niere," p. 48: Tübingen, 1865; Meissner, *Zeitschr. f. rat. Med.* (3), vol. xxxi. p. 183: 1867.

[5] *Vide* Paschutin, "Arbeiten aus der physiologischen Anstalt zu Leipzig," p. 197: 1872; and Emminghaus, *ibid.*, p. 50: 1873. [See however remarks in note on p. 218.]

of the blood, to remove which is the duty of the kidneys. This does not necessitate any nervous apparatus.[1]

We should *à priori* expect that the kidneys would be all the more active, the more substances there were in the blood to be excreted, and the greater the amount of blood flowing through the kidneys in a unit of time. All the facts observed agree with this view. Whatever enlarges the lumen of the renal vessels and increases the rapidity of the blood-current, such as section of the splanchnic nerve and stimulation of the spinal cord, also increases the quantity of urine secreted. Whatever causes contraction of the vessels and diminishes the rapidity of the current, as stimulation of the splanchnic, mechanical narrowing of the renal artery, or section of the cervical spinal cord, also diminishes the urine. There is at present no ground for assuming that the blood-pressure in the renal vessels has a direct influence upon the secretion of urine.

From these observations on the functions of the kidneys, it follows that the COMPOSITION OF URINE must necessarily be a very varying one. Besides the nitrogenous end-products, the amount of which chiefly depends upon the proteid introduced and undergoes great fluctuations, the urine always contains the inorganic salts which remain over from the decomposition of the organic food-stuffs, as well as sulphuric and phosphoric acids, which proceed from the oxidation and splitting-up of the proteids, nucleins, and lecithins; and finally we find in it certain products of metabolism—notably aromatic compounds and oxalic acid—which are oxidized with difficulty and which contain no nitrogen. Besides the substances which occur in large quantities and have been subjected to careful investigation, there are numerous other substances in the urine which are scarcely known, as they occur in such small quantities. There is also a large class of substances which only appear occasionally under certain normal and pathological conditions that are little known; and lastly, we meet with substances of all kinds which have been accidentally introduced either with food or as medicines, and which have not been destroyed in the body.

In order to give an idea of the composition of normal urine, two analyses are appended, which I carried out on the urine of a young man in good health, both when on animal and on vegetable diet.[2] An estimate was made of almost all the con-

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[1] *Vide* W. von Schröder, "Ueber die Wirkung des Caffeins als Diureticum," *Arch. f. exper. Path. u. Pharm.*, vol. xxii. p. 39: 1886.

[2] The literature of physiology, so far as I know, affords no analysis of urine in which all the more important constituents were determined in the same

stituents of the urine which normally occur in any quantity. After two days' exclusive diet of beef, the urine was collected on the second day. The beef eaten was roasted with a little salt, the only beverage being spring water. In the second case the urine was also collected on the second day, after an exclusive diet of wheat-bread, butter, a little salt, and spring water.

COMPOSITION OF TWENTY-FOUR HOURS' URINE AFTER A DIET OF—

	Meat.		Bread.	
Total amount	1672	c.cms.	1920	c.cms.
Urea	67.2	grms.	20.6	grms.
Uric acid	1.398	"	0.253	"
Creatinin	2.163	"	0.961	"
K_2O	3.308	"	1.314	"
Na_2O	3.991	"	3.923	"
CaO	0.328	"	0.339	"
MgO	0.294	"	0.139	"
Cl	3.817	"	4.996	"
SO_3[1]	4.674	"	1.265	"
P_2O_5	3.437	"	1.658	"

Both urines had a strong acid reaction. If we calculate the equivalent of the strong acids and bases, we find that in both the sulphuric acid and the chlorin suffice by themselves to neutralize all inorganic bases:

$$\begin{array}{rl} 3.308\ K_2O &= 2.177\ Na_2O \\ 3.991\ Na_2O &= 3.991\ Na_2O \\ 0.328\ CaO &= 0.364\ Na_2O \\ 0.294\ MgO &= 0.455\ Na_2O \\ \hline & \ 6.987\ Na_2O \end{array} \qquad \begin{array}{rl} 3.817\ Cl &= 3.337\ Na_2O \\ 4.674\ SO_3 &= 3.622\ Na_2O \\ \hline & \ 6.959\ Na_2O \end{array}$$

$$\begin{array}{rl} 1.314\ K_2O &= 0.865\ Na_2O \\ 3.923\ Na_2O &= 3.923\ Na_2O \\ 0.339\ CaO &= 0.376\ Na_2O \\ 0.139\ MgO &= 0.216\ Na_2O \\ \hline & \ 5.380\ Na_2O \end{array} \qquad \begin{array}{rl} 4.996\ Cl &= 4.368\ Na_2O \\ 1.265\ SO_3 &= 0.980\ Na_2O \\ \hline & \ 5.348\ Na_2O \end{array}$$

But, in addition to the sulphuric and hydrochloric acids, the urines contain also considerable amounts of phosphoric and uric, besides some hippuric and oxalic, acids. It would therefore follow that they contain free mineral acids, had not the organism the means about to be detailed of preventing

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specimen. I therefore venture to communicate these analyses, which were undertaken on the occasion of certain experiments relating to metabolism, and which have not yet been published.

[1] The entire amount of, including the conjugated, sulphuric acid, was determined. The urine was boiled with hydrochloric acid and chlorid of barium.

the occurrence of free strong acids in the urine. In the first place, there is the formation of ammonia. In the above analyses the ammonia has, unfortunately, not been determined. Normal urine generally contains from 0.4 to 0.9 grm. In order to convert the 1.66 grm. of phosphoric acid into the acid ammonia salt, exactly 0.4 grm. of NH_3 suffice; 0.8 grm. of ammonia are equivalent to 3.44 grms. of phosphoric acid. A second mode of diminishing the acidity of the urine consists in a portion of the dibasic sulphuric acid being converted into a monobasic acid by union with aromatic compounds.

Normal urine becomes alkaline only after a vegetable diet containing potash salts of combustible acids. These are largely present in acid fruits and berries which contain the acid potash salts of tartaric, citric, malic, and other organic acids. After combustion of the acids, the potash appears in urine as a carbonate. The urine exhibits a strong alkaline reaction, and effervesces on the addition of acids. Potatoes cause a strongly alkaline urine, because they contain little proteid and therefore little sulphuric acid; on the other hand, they contain much malate of potash, which is converted into a carbonate. The most important articles of vegetable diet, the cereals and the leguminosæ, yield urine which is as acid as that due to a diet of meat, because they are rich in proteid and phosphates.

These observations afford some hints as to the diet of persons who are predisposed to the formation of uric acid, gravel, and concretions in the bladder. I have already shown that we are not fully acquainted with all the conditions of the precipitation of uric acid; but we do know that the acidity of the urine has to be considered as well as the amount of uric acid. Patients should be forbidden food rich in proteid, and poor in bases which are able to neutralize the uric and sulphuric acids formed from the proteid. Cheese appears to me in this respect the most injurious article of food. In making cheese, the basic alkaline salts pass into the whey, and the casein, on undergoing combustion in the organism, yields large quantities of uric, sulphuric, and phosphoric acids, which are not sufficiently neutralized by bases. In certain parts of Saxony, as in Altenburg, where the people eat a great deal of cheese, uric acid calculi are said to be very common.[1] Calculus is rare in Switzerland, although cheese is also an important article of diet there, probably for the reason that a

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[1] Lehmann, *Sitzungsber. der Ges. f. Natur und Heilkunde zu Dresden*, p. 56: 1868; W. Ebstein ("Die Natur und Behandlung der Harnsteine," pp. 145–156; Wiesbaden, 1884) gives a full account of the geographical distribution of calculi.

considerable quantity of fruit is eaten at the same time. The ingestion of salt meat and salt fish also causes a very acid urine containing much uric acid, because, in the process of salting, the basic salts (basic phosphates and carbonates of the alkalies) pass into the lye, and are replaced by neutral chlorid of sodium. Russian physicians have informed me that in certain districts of their country, the people living mainly on salt fish frequently exhibit uric acid calculi. If it be desired to prevent the formation of uric acid sediments, or to dissolve concretions that are already formed, by the administration of alkalies, it is more sensible to advise the use of fruits and potatoes than to order alkaline mineral waters, the continued use of which may produce disturbances which we are unable to estimate. Because the combination of uric acid and lithia is more soluble in water than its combination with soda or potash, it has been thought necessary to treat the uric acid diathesis with a few decigrammes of carbonate of lithia, or even with mineral waters containing one centigramme of lithia to the liter. This naïve idea simply implies ignorance of Berthollet's law. We know that, in solutions of bases and acids, every acid is distributed to all the bases in proportion to their quantity. It follows that only the very smallest portion of uric acid will combine with the lithia, the largest proportion combining with the preponderating quantity of soda, which we introduce as chlorid of sodium. The largest proportion of lithia will reappear in the urine, united with the chlorin of the chlorid, with sulphuric and phosphoric acids. There will be no increase in the solubility of the uric acid.

It is well known that under pathological conditions urine may become alkaline, by the conversion of urea into carbonate of ammonia. This change always takes place when urine has been exposed to the air for some time, and is effected by certain forms of bacteria.[1] If these organisms reach the bladder, the conversion may begin there; the urine becomes alkaline, and the alkaline earths, which were held in solution in the acid urine, are precipitated as phosphate of lime and triple

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[1] P. Cazeneuve et Ch. Livon, *Compt. rend.*, vol. lxxxv. p. 571 : 1877 ; R. von Jaksch, *Zeitschr. f. physiol. Chem.*, vol. v. p. 395 : 1881 ; W. Leube, *Sitzungsber. d. phys. med. Soc. zu Erlangen*, Nov. 10, 1884, p. 4 ; and Virchow's *Arch.*, vol. c. p. 540 : 1885. The ferment may be extracted from the bacteria, but during life they do not yield it to the surrounding fluid (Musculus, *Compt. rend.*, vol. lxxviii. p. 132 : 1874 ; and Pflüger's *Arch.*, vol. xii. p. 214 : 1876 ; A. Sheridan Lea, *Journ. of Physiol.*, vol. vi. p. 136 : 1885). It appears therefore that in the conversion of urea into carbonate of ammonia, chemical potential energy is converted into kinetic energy, and this kinetic energy is used in the vital processes by the fermentative organisms.

phosphate of magnesia. In this way urinary calculi may be formed.

We have now become acquainted with all the ingredients of any importance constituting normal urine. Of the innumerable substances which, besides these, are found in small quantities, I will describe a few, so far as we have any definite knowledge of their origin and significance.

First, the COLORING MATTERS. Physicians have long observed the remarkable differences in the color of urine under various normal and pathological conditions, and have tried to avail themselves of these differences for diagnostic purposes. The numerous endeavors to isolate the coloring matters and to study their properties led to no results, because the quantity was always too small. We have therefore been obliged to content ourselves with applying Greek and Latin names to these numerous pigments, with which I will not trouble the reader, excepting with regard to the only one of which we know the composition and mode of origin. I refer to UROBILIN, which was discovered by Jaffé.[1] He found this reddish brown coloring matter constantly in normal urine, and in increased quantities in febrile urine. Its absorption-spectrum and the green fluorescence which its ammoniacal solution assumes, especially after the addition of chlorid of zinc, are characteristic. The composition of this pigment, which can only be obtained in very small quantities from urine, would not have been known had not Maly[2] succeeded in producing it artificially by the action of nascent hydrogen upon bilirubin, the chief coloring matter of bile.[3] This fully explains the invariable presence of urobilin in the contents of the intestine, as we have seen that nascent hydrogen constantly acts there upon the bile-pigment. Human feces are colored brown chiefly by urobilin, and rarely contain any unaltered bile-pigment. It is quite possible that the urobilin occurring in urine is also derived from the intestine, though we are not forced to this assumption, as urobilin might also be formed in other organs. As a matter of fact, Jaffé found urobilin in human bile. Hoppe-Seyler[4] has since shown that urobilin may also be

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[1] M. Jaffé, Virchow's *Arch.*, vol. xlvii. p. 405: 1869; and *Centralbl. f. d. med. Wissensch.*, p. 241: 1868; p. 177: 1869: and p. 465: 1871.

[2] R. Maly, *Centralbl. f. d. med. Wissensch.*, No. 54: 1871; *Annal. d. Chem.*, vol. clxiii. p. 77: 1872.

[3] [It has been shown by Garrod and Hopkins (*Journ. Physiol.*, vol. lxxii. p. 451: 1897) that in spite of the close similarity in physical characters, the urobilin of urine and feces has a different constitution to that of the hydrobilirubin of Maly. Whereas the latter contains about 9 per cent. nitrogen, urobilin only contains about 4 per cent.]

[4] Hoppe-Seyler, *Ber. d. deutsch. chem. Ges.*, vol. vii. p. 1065: 1874.

formed by the action of nascent hydrogen upon hematin. We thus arrive at a simple genetic connection between the three coloring matters:[1]

Hematin	$C_{32}H_{32}N_4O_4Fe$
Bilirubin	$C_{32}H_{36}N_4O_6$
Urobilin [or, rather, hydrobilirubin]	$C_{32}H_{40}N_4O_7$

INDIGO[2] is generally regarded as belonging to the urinary coloring matters, although it does not occur as such in urine, but as a colorless compound, as an alkaline indoxyl-sulphate.[3] If concentrated hydrochloric acid, with an oxidizing agent like chlorid of lime or bromin water, be added to urine, the conjugated sulphuric acid is split up, and the indoxyl is oxidized into indigo:

$$\underset{\text{Indoxyl-sulphate of potash.}}{2C_8H_6NKSO_4} + O_2 = \underset{\text{Indigo blue.}}{C_{16}H_{10}N_2O_2} + 2HKSO_4$$

The amount of indigo thus formed is generally very small, but is seldom entirely absent from human urine. On shaking the coloring matter with chloroform, a beautiful blue solution is obtained.

We are not in doubt as to the origin of indigo in the animal body, since we know that indol, which is the basis of the entire indigo-group, is obtained by bacterial putrefaction of proteid, and is uniformly found in the intestinal contents.[4] The reabsorbed indol is oxidized in the tissues into indoxyl. This process is completely analogous to the conversion of benzol by oxidation into phenol.

$$\underset{\text{Indol.}}{C_8H_7N} + O = \underset{\text{Indoxyl.}}{C_8H_6(OH)N}$$

Indoxyl combines, like most of the aromatic hydroxylized compounds (phenol, cresol, pyrocatechin, etc.), with sulphuric acid, undergoing dehydration (p. 256). Jaffé[5] showed that, after the subcutaneous injection of indol, the conjugated indoxyl compound reappears copiously in the urine.

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[1] This genetic connection is more fully discussed in the next lecture, as well as the appearance of blood and bile-pigments in the urine under pathological conditions.

[2] On the synthesis and chemical constitution of indigo, *vide* A. Baeyer, *Ber. d. deutsch. chem. Ges.*, vol. xiii. p. 2254: 1880; and vol. xiv. p. 1741: 1881.

[3] E. Baumann and L. Brieger, *Zeitschr. f. physiol. Chem.*, vol. iii. p. 254: 1879. The older literature on the indigo-forming substance of the urine is appended.

[4] S. Radziejewsky, Du Bois' *Arch.*, p. 37: 1870; W. Kühne, *Ber. d. deutsch. chem. Ges.*, vol. viii. p. 206: 1875; Nencki, *ibid.*, vol. viii. p. 336: 1875; Salkowski, *Zeitschr. f. physiol. Chem.*, vol. viii. p. 417; and vol. lxxii. p. 8: 1884.

[5] M. Jaffé, Virchow's *Arch.*, vol. lxx. p. 72: 1877.

In cases of intestinal obstruction a larger quantity of the indoxyl compound has been found in the urine. It is quite possible that this occurrence of large quantities of indigo might be utilized for diagnosis, by enabling us to determine in which section of the intestine the obstruction had taken place. Jaffé has shown, for instance, that the increase in the secretion of indoxyl occurred in dogs after ligature of the small, but not after ligature of the large, intestine. This is explicable from the fact that proteid, which yields the material for the formation of indol, is absorbed before reaching the large intestine. When the small intestine is ligatured, the proteid stagnates and undergoes putrefaction. Corresponding with this, Jaffé has observed an increased excretion of the indoxyl compound in man occurring only in obstruction of the small, and not in fecal obstruction of the large, intestine. This is explained by the fact that the proteids, which furnish the indol by their putrefaction, are all absorbed before they reach the large intestine. Similarly Baumann has observed an increased excretion of the indoxyl compound in men in cases of obstruction of the small intestine, but never in cases of fecal obstruction of the large intestine.

All the other aromatic compounds which occur in the urine as ETHEREAL SULPHATES arise, like the indol, from putrefaction of proteid in the intestine. Baumann[1] has shown that if a dog's intestine is cleared out and disinfected by the administration of calomel, the ethereal sulphates entirely disappear from the urine. If, on the other hand, the putrefactive processes in the intestine are increased by neutralizing the antiseptic hydrochloric acid of the gastric juice by the administration of calcium carbonate, we get an increased amount of the ethereal sulphate in the urine.[2] We thus see that an estimation of these acids in the urine may be of great value as a means of diagnosis, since we gain an insight into the intensity of the putrefactive changes in the alimentary canal. Thus, for example, if it be wished to disinfect the intestine previous to resecting it, we can determine when this is effected, by noting the time when the ethereal sulphates disappear from the urine.[3]

The question now arises: where and in what organs does

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[1] E. Baumann, "Die aromatischen Verbindungen im Harne und die Darmfäulniss," *Zeitschr. f. physiol. Chem.*, vol. x. pp. 123–133: 1886. We particularly recommend this short and lucid statement of Baumann's to the student.

[2] A. Kast, "Ueb. d. quantitative Bemessung der antiseptischen Leistung des Magensaftes," "Festschr. z. Eröffnung d. neuen allg. Krankenhauses zu Hamburg-Eppendorf": 1889.

[3] A. Kast und H. Baas, *Münchener med. Wochenschrift*, No. 4: 1888.

the conjugation of the aromatic compounds, formed in the intestine, with sulphuric acid take place? This much is certain, that it does not primarily take place in the kidney, for after the administration of phenol, phenolsulphuric acid is found in the blood.[1]

Phenol is a violent poison, but the phenolsulphate does not exert toxic effects. Baumann therefore recommends sulphate of soda as an antidote to phenol-poisoning. He found that when phenol was applied to a dog's skin, the animal bore the poison better and yielded more phenolsulphuric acid, when at the same time sulphate of soda was administered. This would not be intelligible if the combination primarily occurred in the kidney.

Baumann found a much larger amount of ethereal sulphates in the liver than in the blood. This renders it probable that the synthesis occurs in the liver; that the poisonous aromatic compounds reaching it from the intestine are here subject to a transformation into innocuous combinations before entering the general circulation (*vide* Lecture XVIII.).

As yet we have only become acquainted with two sorts of compounds of sulphur as constituents of the urine: the salts of the ordinary dibasic and of the monobasic conjugated sulphuric acids. The quantity of sulphuric acid occurring in the latter form in human urine averages one-tenth of the amount of ordinary sulphuric acid.[2] But there is a much larger number of sulphur compounds in the urine. If urine acidulated with acetic acid is precipitated with chlorid of barium, the ordinary sulphates are precipitated. If we now boil the filtrate, rendered strongly acid by the addition of hydrochloric acid, the ethereal sulphates are broken up, and this portion of sulphuric acid may also be precipitated as a salt of barium. If this filtrate is now evaporated to dryness and fused with saltpeter, we again obtain a considerable amount of sulphuric acid. This third group of sulphur compounds contains from 10 to 20 per cent. of all the sulphur excreted in human urine. In dogs and rabbits, the quantity of these organic compounds of sulphur is much larger.[3] Let us now consider what is really known about these organic sulphur compounds, and their relation on the one hand to proteid, and on the other to sulphuric acid.

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[1] Baumann, Pflüger's *Arch.*, vol. xiii. p. 285: 1876.

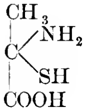
[2] R. v. d. Velden, Virchow's *Arch.*, vol. lxx. p. 343: 1877.

[3] See Voit and Bischoff, "Die Gesetze der Ernährung des Fleischfressers," p. 279: Leipzig, 1860; Voit, *Zeitschr. f. Biolog.*, vol. i. p. 127: 1865; vol. x. note to p. 216: 1874; Salkowski, Virchow's *Arch.*, vol. lviii. p. 460: 1873; Kunkel, Pflüger's *Arch.*, vol. xiv. p. 344: 1877; R. Lépine, Guérin et Flavard, *Revue de Médécine*, vol. i. pp. 27, 911: 1882; St. Bondzynski and R. Gottlieb, *Centralbl. f. d. med. Wissensch.*, No. 33: 1897.

It is not much we know, but we will endeavor to collect and review the fragments of our knowledge.

We are compelled to assume at least two atoms of sulphur in a molecule of proteid, one oxidized and the other unoxidized.[1] If we heat proteid with potash, one sulphur atom goes to form sulphid of potash, the other forms sulphate of potash. The former may be easily recognized on boiling with an alkaline solution of lead oxid when it is precipitated as lead sulphid. The proteids such as casein, the proteid moiety of hemoglobin or legumin, which are poorer in sulphur, do not give this reaction. Among the organic decomposition-products of proteid in the animal body, we meet with the oxidized atom of sulphur in TAURIN, with the unoxidized in CYSTIN. If we boil cystin with an alkaline solution of oxid of lead, a black sulphid of lead is thrown down. Of course taurin, which we have already shown to be amido-ethylsulphonic acid (p. 178), cannot give this reaction.

CYSTIN has the formula $C_3H_6NSO_2$.[2] It does not occur in the normal organism.[3] We are not yet acquainted with the abnormal conditions under which a large amount of the sulphur is secreted in the urine as cystin. It appears however that even in normal metabolism, in the course of the formation of sulphuric acid products, a body is formed which is closely allied to cystin, and is distinguished from it only by an additional atom of hydrogen, *viz.*, cystein. A substituted cystein, for instance, appears in the urine of dogs after the administration of brombenzol. Baumann,[4] to whom we are indebted for the most searching inquiries into the origin of cystin, regards cystein as a lactic acid, in which H is replaced by NH_2, and the OH by SH—



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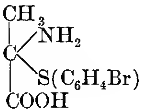
[1] The latest and most careful researches on the condition of the sulphur in proteids have been carried out by A. Krüger (Pflüger's *Arch.*, vol. xliii. p. 244: 1888). Unfortunately, Krüger did not make use of pure material for his researches.

[2] E. Külz, *Zeitschr. f. Biolog.*, vol. xx. p. 1 : 1884.

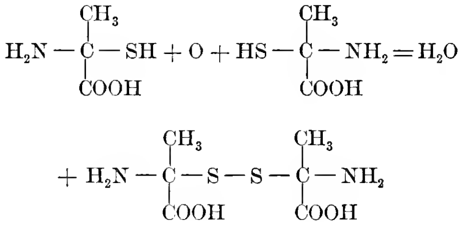
[3] Stadthagen, *Zeitschr. f. physiol. Chem.*, vol. ix. p. 129 : 1884.

[4] E. Baumann and C. Preusse, *Ber. d. deutsch. chem. Ges.*, vol. xii. p. 806 : 1879; *Zeitschr. f. physiol. Chem.*, vol. v. p. 309 : 1881; M. Jaffé, *Ber. d. deutsch. chem. Ges.*, vol. xii. p. 1092 : 1879; Baumann, *ibid.*, vol. xv. p. 1731 : 1882; *Zeitschr. f. physiol. Chem.*, vol. viii. p. 299 : 1884. *Vide* also E. Goldmann, *ibid.*, vol. ix. p. 260 : 1884.

The substituted cystein which appears in the urine after administration of brombenzol when boiled with dilute acids, is broken up, with hydration, into acetic acid and bromphenylcystein—



Baumann obtained cystein from cystin by the action of nascent hydrogen. The oxygen of atmospheric air reconverts the cystein into cystin.

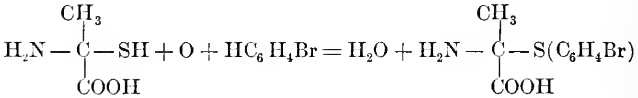


$$\mathrm{H_2N}-\underset{\mathrm{COOH}}{\overset{\mathrm{CH_3}}{\mathrm{C}}}-\mathrm{SH}+\mathrm{O}+\mathrm{HS}-\underset{\mathrm{COOH}}{\overset{\mathrm{CH_3}}{\mathrm{C}}}-\mathrm{NH_2}=\mathrm{H_2O}$$

$$+\ \mathrm{H_2N}-\underset{\mathrm{COOH}}{\overset{\mathrm{CH_3}}{\mathrm{C}}}-\mathrm{S}-\mathrm{S}-\underset{\mathrm{COOH}}{\overset{\mathrm{CH_3}}{\mathrm{C}}}-\mathrm{NH_2}$$

The empirical formula of cystin must therefore be doubled: $C_6H_{12}N_2S_2O_4$. The origin of cystin in the animal body is probably due to a synthetic process, and possibly two molecules of proteid always yield the material for the formation of one molecule of cystin.

The formation of bromphenylcystein would accordingly be a process quite analogous to that of cystin. Here again a divalent oxygen atom takes a hydrogen atom from cystin and from brombenzol, and effects the linking of the liberated affinities—



$$\mathrm{H_2N}-\underset{\mathrm{COOH}}{\overset{\mathrm{CH_3}}{\mathrm{C}}}-\mathrm{SH}+\mathrm{O}+\mathrm{HC_6\,H_4Br}=\mathrm{H_2O}+\mathrm{H_2N}-\underset{\mathrm{COOH}}{\overset{\mathrm{CH_3}}{\mathrm{C}}}-\mathrm{S(C_6H_4Br)}$$

Cystin does not dissolve readily in water, it therefore always occurs in urine as a sediment, and very occasionally causes the formation of vesical calculi. There are some people who secrete a large quantity (about one-quarter) of the sulphur as cystin, without exhibiting any derangement in their health. This rare anomaly of metabolism sometimes occurs, probably as the result of heredity, in several members of the same family.[1]

Under normal conditions cystin, or its antecedent cystein, breaks up still further and is oxidized, and the greater portion of its sulphur appears in the urine as sulphuric acid. This is confirmed by an experiment made in Baumann's laboratory by Goldmann.[2] He gave a little dog 2 grms. of cystein, and found that the greater portion, about two-thirds, appeared as sulphuric acid in the urine. The remainder had served to increase the organic sulphur compounds in the urine. This view, that the larger portion of the sulphur of cystein is converted by oxidation into sulphuric acid, is confirmed by the fact that in the cystinuria of man, the urine has generally an alkaline or very feebly acid reaction.

We know little positively with regard to the fate of TAURIN [$CH_2(NH_2) - CH_2SO_3H$]. I have already stated that the amount of sulphur which occurs as taurin in bile constitutes only a minute portion of the sulphur of the decomposed proteid, and is only slightly increased if more proteid is taken (compare p. 182). It is questionable therefore whether a taurin molecule results from each molecule of proteid. In bile, taurin is conjugated with cholalic acid. In the intestine, the ferments of digestion and putrefaction doubtless cause this compound to break up with hydration. We do not know whether the liberated taurin is absorbed as such, or after previous change. We have not been able as yet to prove its presence in the feces or in the urine. No satisfactory results have been obtained with regard to the further destination of taurin from experiments[3] consisting in its artificial introduction into the body. If large quantities of taurin are administered to man or dogs, the process of absorption does not take place slowly enough to allow of its complete change into the normal end-products; one portion of the taurin appears as such in the urine, another as a substituted urea—

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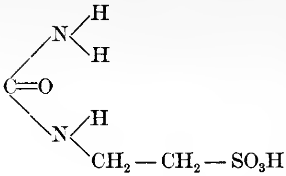
[1] F. W. Beneke, "Grundlinien der Pathologie des Stoffwechsels," p. 255: Berlin, 1874. Compare also A. Niemann, *Deutsch. Arch. f. klin. Med.*, vol. xviii. p. 232: 1876; W. F. Löbisch, Liebig's *Annal.*, vol. clxxxii. p. 231: 1876; W. Ebstein, "Die Natur und Behandlung der Gicht," p. 130: Wiesbaden, 1882; and "Die Natur und Behandlung der Harnsteine," p. 172: Wiesbaden, 1884; Stadthagen, Virchow's *Arch.*, vol. c. p. 416: 1885.

[2] E. Goldmann, *Zeitschr. f. physiol. Chem.*, vol. ix. p. 269: 1885.

[3] E. Salkowski, *Ber. d. deutsch. chem. Ges.*, vol. vi. pp. 744, 1191, 1312: 1873; and Virchow's *Arch.*, vol. lviii. p. 460: 1873.



The presence of this substituted urea has not so far been positively demonstrated in normal urine. In the rabbit, it is not found even after the artificial introduction of taurin. Almost all the sulphur of the taurin reappears as sulphuric and THIOSULPHURIC acid in the urine of these animals. The conversion into thiosulphuric acid however occurs only when the taurin is introduced into the stomach; if it is injected subcutaneously, the greater part reappears unaltered in the urine. The thiosulphuric acid is evidently formed by the processes of reduction taking place in the intestine. In the normal urine of rabbits, thiosulphuric acid has not been found, though it occurs frequently in that of cats and dogs.[1] In human urine, it has only been once found in typhoid.[2]

SULPHOCYANIC ACID,[3] (CNSH), also belongs to the sulphur compounds occurring in the urine. Gscheidlen found these acids constantly in human urine, and in that of horses, cattle, dogs, cats, and rabbits. On an average, one liter of human urine contained 0.02 grm. Munk found the average of three determinations to be 0.08 grm. Sulphocyanates were also found in dogs' blood. Gscheidlen proved that they are derived from the salivary glands. The saliva of mammals invariably contains small quantities of sulphocyanates. Gscheidlen and Heidenhain divided all the ducts of the salivary glands in dogs, and thus prevented the saliva from entering the mouth. The alkaline sulphocyanate was now found to have disappeared from the blood and the urine; although it was still present in the saliva flowing from the wounds. It follows that in the normal condition sulphocyanic acid is formed in the salivary glands, passes with the saliva into the intestinal canal, whence it is absorbed into the blood and appears in the urine. We

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[1] O. Schmiedeberg, *Arch. d. Heilk.*, vol. viii. p. 422: 1867; Meissner, *Zeitschr. f. rat. Med.*, vol. xxxi. p. 322: 1868.

[2] Ad. Strümpell, *Arch. d. Heilk.*, vol. xvii. p. 390: 1876.

[3] Leared, *Proc. Roy. Soc.*, vol. xvi. p. 18: 1870; Gscheidlen, *Tageblatt d. 47 Vers. d. Naturf. u. Aerzte in Breslau*, p. 98: 1874; and Pflüger's *Arch.*, vol. xiv. p. 401: 1877; Külz, *Sitzungsber. d. Ges. z. Beförder. d. ges. Naturw. in Marburg*, p. 76: 1875; J. Munk, Virchow's *Arch.*, vol. lxix. p. 354: 1877.

are ignorant as to the significance of these small quantities of sulphocyanic acid in the functions of the saliva, or in any other processes of the organism.

Of the organic constituents of the urine, only those which are free from sulphur and nitrogen remain for our consideration. LACTIC ACID, SUGAR and OXALIC ACID belong to this class. Lactic acid however has never been detected with certainty in normal urine. It has only been found in phosphorus-poisoning, atrophy of the liver,[1] osteomalacia,[2] and trichinosis.[3] On teleological grounds, we must doubt whether lactic acid passes into normal urine, as this would be a waste of potential energy. The same argument applies in a still more forcible manner to sugar. All analyses of normal urine have the more positively shown the absence of sugar, the more carefully the investigation was carried out. Even those writers who assert the presence of sugar in normal urine, admit that they have only succeeded in finding it in very minute quantities.[4]

OXALIC ACID is a constant ingredient in normal human urine after a mixed diet, but it never occurs except in very small quantity, at most 0.02 grm. in twenty-four hours' urine.[5] This oxalic acid, in all probability, arises from the oxalic acid which is contained in the vegetable articles of food. There is at present no sufficient reason for assuming any other source for the oxalic acid of normal urine. I was unable to detect any oxalic acid in the urine of a young man in good health after two days' exclusive diet of meat, nor in the urine of another healthy young man after he had eaten nothing but fat meat and sugar.[6] It therefore appears that oxalic acid does not normally arise from any of the three main classes of

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[1] Schultzen and Riess, *Annalen des Charité-Krankenhauses*, vol. xv.: 1869.

[2] Moers and Muck, *Deutsch. Arch. f. klin. Med.*, vol. v. p. 485 : 1869. The method of testing used in this experiment was, however, unsatisfactory. Compare the critique of Nencki and Sieber, *Journ. f. prakt. Chem.*, vol. xxvi. p. 41 : 1882; and E. Heuss, *Arch. f. exper. Path. u. Pharm.*, vol. xxvi. p. 147: 1889.

[3] Th. Simon und F. Wibel, *Ber. d. deutsch. chem. Ges.*, vol. iv. p. 139 : 1871.

[4] In this connection see E. Külz, Pflüger's *Arch.*, vol. xiii. p. 269 : 1876; M. Abeles, *Centralbl. f. d. med. Wissensch.*, Nos. 3, 12, 22 : 1879; J. Seegen, *ibid.*, Nos. 8, 16; Regulus Moscatelli, Moleschott's *Unters. zur Naturlehre des Menschen u. d. Th.*, vol. xiii. p. 103 : 1881; L. v. Udranszky, *Zeitschr. f. physiol. Chem.*, vol. xii. p. 377 : 1888 ; and *Bericht. d. naturforsch. Gesellsch. z. Freiburg i. B.*, vol. iv. part v.: 1889. Compare the works quoted on pp. 259, 260, on glycuronic acid.

[5] P. Fürbringer, *Deutsch. Arch. f. klin. Med.*, vol. xviii. p. 143 : 1876; an account of the literature on the excretion of oxalic acid is given here. Fürbringer adopted Neubauer's method. O. Schultzen (Du Bois' *Arch.*, p. 719 : 1868) found higher values by employing another method. A critique of both methods is given by Wesley Mills, whose researches on the subject were carried out under Salkowski, Virchow's *Arch.*, vol. xcix. p. 305 : 1885.

[6] I made use of Neubauer's method in testing for it.

food. But the oxalic acid contained in vegetable articles of diet must pass into the urine. Experiments carried out by Gaglio[1] in Schmiedeberg's laboratory at Strassburg show that oxalic acid is not destroyed in the animal body. No oxalic acid was excreted either by a dog that was starving or by one that was fed on meat.[2] But if only from ½ to 1 mgrm. of oxalic acid or of oxalate of soda was injected subcutaneously, the presence of oxalic acid was demonstrated in the urine within the next twenty-four or forty-eight hours. If a neutral solution of oxalate of soda was injected into the crop of a cock, nearly all the oxalic acid was found in the discharge of the cloaca.

Somewhat different conclusions were arrived at by P. Marfori,[3] who took 1 to 1.5 grms. oxalic acid and determined the amount of this substance excreted in the feces and urine. Only a small portion of the oxalic acid reappeared in the feces. So that the greater part was absorbed. Of the amount absorbed, only 4 to 14 per cent. could be recovered from the urine.

It seems however that, under abnormal conditions,[4] oxalic acid may appear as the result of metabolism, owing to an imperfect oxidation of articles of diet. Medical literature contains numerous cases illustrating increased excretion of oxalic acid in jaundice, diabetes, scrofula, hypochondriasis, and other disorders. We even find oxaluria spoken of as an independent disease. But we seek in vain for trustworthy quantitative determinations, with due consideration of the constituents of the food. The conditions underlying the occurrence of oxalic acid in the urine have great practical interest, because oxalic acid may lead to the formation of calculi. The lime salt of this acid is well known to be insoluble in water; hence this salt is frequently to be found in urinary sediments in the well-known octahedral form. If the oxalate is precipitated in the

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[1] Gaetano Gaglio, *Arch. f. exper. Path. u. Pharm.*, vol. xxii. p. 246: 1887.

[2] In contradiction to this account of Gaglio's, we find it stated by W. Mill (Virchow's *Arch.*, vol. xcix. p. 305: 1885) that he detected minute quantities of oxalic acid in the urine of dogs fed exclusively on meat or on meat and bacon.

[3] Pio Marfori, "Sulle trasformazioni di alcuni acidi della serie ossalica nel organismo dell'uomo," Milano, 1890.

[4] In this respect we should note the statements of Gaglio, who uniformly found oxalic acid in the urine of frogs, when he arrested their muscular movements by destruction of the spinal cord, by paralyzing poisons, or by mere fixation (*Giornale della R. Accad. di Med. di Torino*, p. 178: 1883); and also those of Hammerbacher, who found the excretion of oxalic acid increased in dogs after the administration of bicarbonate of soda (Pflüger's *Arch.*, vol. xxxiii. p. 89: 1883). This effect of bicarbonate of soda was not confirmed by Fürbringer (*loc. cit.*) in man.

bladder, it may lead to the formation of vesical calculi. The solution of oxalate of lime in the urine depends mainly on its acidity. A solution of acid phosphate of soda dissolves oxalate of lime.[1] We can thus explain how it is that oxalate calculi sometimes form under similar conditions as phosphatic calculi, and that occasionally vesical calculi consist of both ingredients, mixed up together or in concentric layers. I wish again to lay stress on the fact that increase in the sediment of oxalate of lime does not justify the inference that there is an increased secretion of oxalic acid. This erroneous conclusion has led to many mistakes.

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[1] C. Neubauer, *Arch. des Vereins für gemeinschaftliche Arbeiten zur Förderung der wissenschaftlichen Heilkunde*, vol. iv. pp. 16, 17: 1858; and Moddermann, *Nederl. Tijdschr.:* 1864, summarized in Schmidt's *Jahrbücher der gesammten Med.*, vol. cxxv. p. 145: 1865.

LECTURE XXII

METABOLISM IN THE LIVER—FORMATION OF GLYCOGEN

We now approach one of the most involved and difficult subjects in the whole range of physiological chemistry: the metabolism in the liver.

Like the kidney, the liver has to fulfil the function of maintaining the uniform composition of the blood. While the kidney removes all superfluous and foreign ingredients, the liver revises everything before it enters the blood. For this reason, it is interposed in the current that passes from the intestine to the heart. We have seen how it guards against the blood being overwhelmed with sugar, while, on the other hand, it prevents a deficiency of this important article of nutrition in the blood (p. 189). We have also seen that it is constantly converting ammonia, which is a virulent poison, into harmless compounds, such as urea and uric acid (pp. 294, 310). Similarly, the liver converts the equally poisonous aromatic products of putrefaction, which originate from the proteids in the intestine, into harmless compounds, by conjugation with alkaline sulphates (pp. 256, 326). We also know that many poisons, such as metals, alkaloids,[1] etc., are arrested in the liver.

It also appears that the system of innervation of the liver is identical with that of the kidney. We have not hitherto been able to prove a direct influence of nerves upon the hepatic cell. The functions of the liver, like those of the kidney, are regulated directly by the composition of the blood. This fact also indicates that the chief duty of the liver consists in regulating the composition of the blood (compare p. 189).

In addition to this function, the liver, as we have seen above, performs that of secreting bile. We have already mentioned the grounds for our belief that bile is not merely an accidental product which is excreted during the essential

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[1] G. H. Roger, *Arch. d. physiol. norm. et path.*, V. vol. iv. p. 24: 1892; E. Kotliar, *Arch. d. Sc. biol.*, vol. ii. p. 586: 1893.

changes taking place in the liver, and removed by the intestine, but that is a secretion which performs important duties in the processes occurring in the bowel (*vide supra*, pp. 182–186).

All these facts tend to show that the liver, the largest of all glands, is the seat of numerous and complex chemical changes. It has been hoped, by comparing the composition of the inflowing and outflowing blood, to obtain an insight into these processes, or at least to suggest certain fruitful inquiries. Numerous comparative analyses have been made of the blood in the portal and hepatic veins.[1] But when we consider how large a quantity of blood passes through the liver, and how trifling the amount of bile and lymph formed is in comparison, we can scarcely expect to be able to demonstrate marked differences in the composition of the inflowing and outflowing blood. It is probable that the differences in the analyses of the blood of the portal and hepatic veins are due to experimental errors, for they have been smaller in proportion to the care bestowed on the analyses, and, in the most reliable determinations, are within the limits of unavoidable errors.

Another method of obtaining an insight into the processes occurring in the liver would consist in extirpating that organ, or at least in isolating it from the circulation of the blood, and noticing what changes take place in the animal metabolism as a result of the operation. In this way we might hope, in the first instance, to decide whether the constituents of bile, the bile acids and pigments, are formed in the liver or are conveyed to it by the blood. If the latter were the case, the liver would be only an excretory organ, and its extirpation would cause an accumulation of the biliary constituents in the blood and in the organs.

We have already seen, when discussing the question as to the locality of the formation of hippuric acid, that frogs survive the extirpation of the liver for several days, but the experiments which have been carried out with reference to the present question, have been inconclusive, because the inquirers were unable to overcome the difficulties which present themselves in the endeavor to demonstrate the constituents of bile in the organs of the frog.[2]

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[1] C. Flügge gives a critical account of these works, *Zeitschr. f. Biolog.*, vol. xiii. p. 133: 1877; compare also W. Drosdoff, *Zeitschr. f. physiol. Chem.*, vol. i. p. 233: 1877.

[2] These experiments are criticised by Hans Stern, *Arch. f. exper. Path. u. Pharm.*, vol. xix. pp. 42–44: 1885. None of the investigators has proved, by control experiments, that he can demonstrate small quantities of biliary constituents in frog's tissue.

I have already repeatedly mentioned that, on account of the accumulation of blood in the portal system after extirpation or isolation of the liver in mammals, this operation has not as yet been successful in them (p. 295). In discussing the formation of uric acid, we have seen that this difficulty does not present itself in birds, owing to their possessing a normal communication between the portal and renal veins (p. 310). Naunyn, Stern, and Minkowski have utilized this circumstance, in order to determine the question as to the seat of the formation of the biliary constituents in birds.

Stern[1] ligatured the bile-ducts and all the vessels passing to the liver in pigeons, including not only the portal vein and the hepatic artery, but also the small veins. After from ten to twenty-four hours, the animals were bled to death. No secretion of urine had taken place after the operation, as renal activity always ceases in pigeons after ligaturing the liver.[2] If the biliary constituents were formed outside the liver, they would now accumulate in the blood and in the tissues, as they would have no exit. Stern paid special attention to the bile pigment, which is easy of detection; but it was nowhere to be found, not even in the serum on the application of Gmelin's very delicate test, nor in any tissues or organs; there was no icteric discoloration anywhere. On the other hand, if in pigeons the bile-ducts only were ligatured, bile pigment was found after an hour and a half in the urine, and with perfect certainty in the serum after five hours. It follows, from these valuable inquiries, that the coloring matter of bile is formed in the liver.

The same applies to the bile acids. This has already been proved by an inquiry carried out by Fleischl[3] in Ludwig's laboratory. Bile acids cannot be shown to exist in normal blood.[4] If the bile-duct be ligatured, the biliary constituents pass into the lymphatics of the liver, and thence direct through

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[1] Hans Stern, *Arch. f. exper. Path. u. Pharm.*, vol. xix. p. 39: 1885.

[2] Fowls, ducks, and geese continue to secrete urine after the liver has been ligatured and extirpated (Minkowski and Naunyn, *Arch. f. exper. Path. u. Pharm.*, vol. xxi. p. 3: 1886).

[3] E. Fleischl, *Ber. d. k. sächs. Ges. d. Wissensch.*, Math.-physikal.-Klasse, Sitzung vom 8 Mai, p. 42: 1874. *Vide* also Kufferath, Du Bois' *Arch.*, p. 92: 1880, and V. Harley, *ibid.*, p. 292: 1893.

[4] We must however assume that traces of bile acids do occur in normal blood, as they are absorbed from the intestine. Dragendorff (*Zeitschr. f. anal. Chem.*, vol. xi. p. 467: 1872) and Joh. Hone (Dissert.: Dorpat, 1873) found traces in normal human urine. Hoppe-Seyler and L. v. Udranszki dispute this statement (*Zeitschr. f. physiol. Chem.*, vol. xii. p. 375: 1888).

the thoracic duct into the blood. If, after ligaturing the bile-duct, a cannula be introduced into the thoracic duct so as to collect the chyle, bile acids may be shown to be contained in it. If the bile-duct and the thoracic duct be ligatured at the same time, the latter becomes distended with lymph, but no trace of bile acids can be found in the blood.

The observations of Minkowski and Naunyn[1] perfectly harmonize with the results obtained by Fleischl, as after shutting out the liver from the circulation, they were never able to detect bile acids in the blood.

We may therefore conclude that the specific constituents of the bile acids and pigments are formed in the liver.

We now come to the question as to the origin of the specific biliary constituents. With regard to the bile acids, their nitrogenous moieties, glycocol and taurin, are doubtless derived, as I have already shown (pp. 177, 288), from proteid. Cholalic acid, which is non-nitrogenous, does not necessarily originate in the same material. It is conceivable that it may be derived from another source, and subsequently combine with the nitrogenous compounds by a process of synthesis, with loss of water; this would be entirely analogous to the mode of formation of hippuric acid. We should note the small amount of hydrogen contained in cholalic acid (p. 177). If it be formed from fats or carbohydrates, the carbon atoms of the molecule must become linked by two bonds of affinity instead of one, as in the case of these two classes. This would only be a further proof that syntheses occurring in the animal are as complicated as those occurring in the vegetable cell.

The coloring matter of bile, bilirubin (*vide* p. 323), almost certainly arises from the coloring matter of the blood, hematin. The following facts support this view.

Bile pigments are found only in animals whose blood contains hemoglobin, *i. e.*, the vertebrata. The invertebrata have not hitherto been shown to possess them. It might be objected that this depends upon some other peculiarity of the vertebrata, as blood-cells containing hemoglobin are not the sole feature which distinguishes the vertebrata from the invertebrata. With regard to this, it is interesting to observe that the amphioxus, which has no red blood-corpuscles, but which from its whole structure, belongs to the vertebrata, forms no bile pigment. Hoppe-Seyler[2] has searched for it without success.

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[1] Minkowski and Naunyn, *Arch. f. exper. Path. u. Pharm.* vol. xxi. p. 7: 1886.

[2] Hoppe-Seyler, Pflüger's *Arch.*, vol. xiv. 399: 1877.

It is well known that the liver of the amphioxus is a mere cecal appendage of the intestine, the gland being only indicated as in the embryos of the higher vertebrata.

It is almost certain that there is a genetic relation between bile pigments and hematin, if we compare their constitution (compare pp. 178, 323)—

Hematin	$C_{32}H_{32}N_4O_4Fe$.
Bilirubin	$C_{32}H_{36}N_4O_6$.
Biliverdin	$C_{32}H_{36}N_4O_8$.

Hematoporphyrin, a pigment isomeric with bilirubin, can be artificially prepared from hematin by treatment with hydrobromic acid.[1]

The following fact may also be brought forward as an argument: in extravasations of blood the coloring matter of the blood disappears, and in place of it we find a crystallized pigment, which Virchow[2] was the first to examine carefully, and named hematoidin. The same writer pointed out its resemblance to bile pigment. Subsequently Robin,[3] Jaffé,[4] and Salkowski[5] proved the identity of hematoidin and bilirubin. Langhans[6] took the blood from the vein of a living pigeon and injected it under the skin of the same animal; after two or three days the coloring matter of the blood had disappeared from the subcutaneous clot, and was replaced by bilirubin and biliverdin. Quincke[7] performed the same experiment on dogs. In this case the conversion occupied more time; the bilirubin did not appear in the subcutaneous injection before the ninth day. Cordua[8] injected blood into the abdominal cavity of dogs, and found bilirubin after so short a time as thirty-six hours. Finally, Recklinghausen[9] has seen bile pigment formed in the blood of frogs outside the body after from three to ten days.

Our clinical experience entirely accords with these experiments upon animals, for we see that after hemorrhages under

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[1] M. Nencki and N. Sieber, *Sitz. d. K. Akad. d. Wissensch. i. Wien*, Math.-nat.-Klasse, vol. xcvii. pt. 2: 1888.

[2] Virchow in his *Arch.*, vol. i. pp. 379, 407: 1847.

[3] Robin, *Compt. rend.*, vol. xli. p. 506: 1855. Robin obtained 3 grms. of hematoidin crystals from an hepatic cyst, and analyzed them.

[4] Jaffé, Virchow's *Arch.*, vol. xxiii. p. 192: 1862.

[5] E. Salkowski, Hoppe-Seyler's *Med. chem. Unters.*, Heft iii. p. 436: 1868.

[6] Th. Langhans, Virchow's *Arch.*, vol. xlix. p. 66: 1870.

[7] H. Quincke, Virchow's *Arch.*, vol. xcv. p. 125: 1884.

[8] Herm. Cordua, "Ueber den Resorptionsmechanismus von Blutergüssen": Berlin, Hirschwald, 1877.

[9] Recklinghausen, "Handbh. der allgem. Patholog. d. Kreislaufes und der Ernährung," p. 434: Stuttgart, Enke, 1883.

the most varied conditions (in cerebral hemorrhage, in pulmonary infarcts, in hematocele, in extravasations depending upon mechanical injury, in abdominal hemorrhages consequent upon extrauterine pregnancy, in rupture of the sac, &c.), urobilin (*vide* p. 323) the product of the conversion of bilirubin occurs in large quantities in the urine.[1]

Bilirubin is sometimes found in the urine, if from any cause hemoglobin passes out of the blood-corpuscles into the plasma. This may be brought about by the injection of water in large quantity, of chloroform, ether, or glycerin into the blood, or merely by the injection of a solution of hemoglobin.[2] It may however be questioned whether the relation is as simple as it appears, and whether the bile pigment occurring in the urine is formed from the hemoglobin that has passed into the plasma within the circulation. The connection is probably one of an indirect character.[3] The presence of hemoglobin in the plasma sometimes causes only hemoglobinuria, sometimes both hemoglobinuria and bilirubinuria, or, again, bilirubinuria alone; sometimes neither of these occurs. We have not yet satisfactorily settled the conditions under which the unaltered coloring matter of blood or its product is found in the urine.

We have seen that bile pigment is normally formed in the liver, but the observations made upon extravasations of blood show that in abnormal conditions it may also arise elsewhere. Hence it has been asked whether the bile pigment occurring in jaundice is invariably formed in the liver. The most frequent cause of jaundice, which is characterized by the appearance of bile pigment in the tissues and in the urine, is well known to be a narrowing or a complete occlusion of the bile-ducts. This generally occurs at the orifice of the common bile-duct, in consequence of catarrh of the duodenum, or from the presence of biliary calculi, tumors, and the like. In this way the bile is blocked up, and reaches the lymphatics of the liver, passes into the blood through the thoracic duct, and thus into all the tissues and the urine. We term this form obstructive, mechanical, or hepatogenous jaundice. In contrast to this an

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[1] E. von Bergmann, "Die Hirnverletzungen mit allgemeinen und mit Herdsymptomen," in R. Volkmann's *Sammlung klinischer Vorträge*, No. 190 : Leipzig, Breitkopf and Härtel, 1881; B. Dick, *Arch. f. Gynäkologie*, vol. xxiii. p. 1 : 1884. Comp. also G. Hoppe-Seyler, Virchow's *Arch.*, vol. cxxiv. p. 30 : 1891; and vol. cxxviii. p. 43 : 1892.

[2] Kühne, Virchow's *Arch.*, vol. xiv. p. 338: 1858. M. Hermann, "De effectu sanguinis diluti in secretionem urinae," Dissert. inaug.: Berolini, 1859. Nothnagel, *Berl. klin. Wochensch.*, p. 31: 1866. Tarchanoff, Pflüger's *Arch.*, vol. ix. p. 53: 1874.

[3] *Vide* E. Stadelmann, *Arch. f. exper. Path. u. Pharm.*, vol. xv. p. 337: 1882.

an-hepatogenous, hematogenous, or chemical jaundice[1] has been assumed, which was attributed to a conversion of the coloring matter of blood into bile pigment outside the liver. A case was assigned to the latter class when no definite lesions could be discovered in the liver, and when, the flow of bile into the intestine being apparently unchecked, the feces did not exhibit the "clay color" characteristic of jaundice (compare p. 183); moreover, certain forms of poisoning, as from arseniuretted hydrogen, chloroform, ether, fungi, and certain severe infective diseases, like typhus, malaria, pyemia, gave countenance to this view. In many of these cases a passage of hemoglobin from the blood-corpuscles into the plasma could be directly shown under the microscope. Stromata were also occasionally found in the blood, and hemoglobin was seen to pass into the urine. It was therefore considered that in these cases a portion of the hemoglobin, which had passed into the plasma, had been converted into bilirubin outside the liver.

One might have expected to be able to distinguish the two forms of jaundice by the passage of the bile acids into the urine together with the bile pigments in obstructive but not in hematogenous jaundice. But it is manifest that the bile acids are speedily destroyed after their passage into the blood; even in undoubted obstructive jaundice, their presence in the urine can sometimes not be traced. On the other hand, they are sometimes discovered in small quantities in normal urine (compare p. 336, note 4). Large quantities of bile acids in the urine certainly allow us to conclude that we have to do with obstructive jaundice; but their absence does not justify the inference that we have to deal with the hematogenous form.

More recent research has proved that there is not at present any sound basis for the conclusion that the bile pigment occurring in jaundice has any other source than the liver.

Minkowski and Naunyn[2] removed the liver of a goose, and immediately exposed it, as well as a healthy goose, to the influence of arseniuretted hydrogen. After half an hour, the control goose evacuated urine containing considerable quantities of biliverdin, which continued to be secreted for two days.

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[1] H. Quincke, Virchow's *Arch.*, vol. xcv. p. 125: 1884. Minkowski and Naunyn, *Arch. f. exp. Path. u. Pharm.*, vol. xxi. p. 1: 1886. A critical account of the comprehensive literature on the various forms of jaundice is given by these authors.

[2] Minkowski and Naunyn, *loc. cit.*, p. 18. Compare also Valentini, *Arch. f. exper. Path. u. Pharm.*, vol. xxiv. p. 412: 1888.

On the other hand, the urine of the goose without the liver at first showed only a minute quantity of biliverdin; but after half an hour's exposure to the poison hemoglobin appeared in the urine, and the urine subsequently discharged was perfectly free from bile pigment. The blood also contained neither bilirubin nor biliverdin. It is therefore extremely probable that the bile pigment appearing in the urine after poisoning with arseniuretted hydrogen has its source in the liver.

According to my view, every form of jaundice is induced by obstruction. We must not forget that it is not necessary that the larger bile-ducts should be completely obstructed in order to cause the passage of bile into the blood. The slightest disturbance, the least arrest of the flow from the primary bile-ducts, suffices to induce it.

So long as there is an unimpeded flow into the intestine, the bile pigment follows this route, and does not pass into the urine. Tarchanoff injected a solution of bile pigment directly into the blood of a dog with a biliary fistula, and found an increased secretion of pigment in the bile which proceeded from the fistula; but there was none in the urine.[1] We may therefore assume that whenever bile pigment occurs in the urine, it is a sign of biliary obstruction. The bile pigment which is formed in extravasations of blood reappears in the urine, as already said, not in its original form, but reduced to urobilin. We need not be surprised at such a reduction taking place in the tissues, as we know from the researches of Ehrlich that very energetic processes of reduction occur in many organs and tissues.[2] Ehrlich injected into living animals blue dye-stuffs, as alizarin blue, indophenol blue, which are decolorized by the withdrawal of oxygen. These dyes circulated in the blood-plasma without being altered. But in certain tissues, especially in the connective and adipose tissues, they were decolorized. When an incision was made into the tissues, they at first appeared colorless; the blue color did not appear until the oxygen of the air had operated for some time. Possibly the reducing power of the tissues explains the increased excretion of urobilin which accompanies the fading of jaundice. The bilirubin which had penetrated the tissues during the biliary obstruction now

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[1] Tarchanoff, Pflüger's *Arch.*, vol. ix. p. 332: 1874. Adolf Vossius has confirmed these results by fresh experiments (*Arch. f. exper. Path. u. Pharm.*, vol. xi. p. 446: 1879). *Vide* also A. Kunkel, Virchow's *Arch.*, vol. lxxix. p. 463: 1880.

[2] P. Ehrlich, "Das Sauerstoffbedürfniss des Organismus": Berlin, Hirschwald, 1885.

returns to the blood as urobilin, and passes out through the kidneys into the urine.[1]

The obstruction of the bile which occurs in the jaundice resulting from poisoning by arseniuretted hydrogen is probably caused in the following manner. There is an increased secretion of bile, for the intestine in the poisoned animals is loaded with bile. It is therefore perfectly plausible to assume that the copious inspissated bile cannot discharge itself quickly enough, and that this alone suffices to induce obstruction;[2] for the pressure in the bile-ducts is very slight, and can be overcome by a trifling resistance.[3] Stadelmann[4] has convincingly shown that the jaundice resulting from poisoning by arseniuretted hydrogen or toluylendiamin is due to obstruction. When dogs with biliary fistulæ were poisoned with these substances, there was a great increase of bile in the secretion, which was moreover very thick and tenacious. They never found catarrh of the duodenum, nor occlusion of the common bile-duct, in their numerous autopsies. It was evident that jaudice resulting from the action of toluylendiamin was due to obstruction, from the simple fact that large quantities of bile acids were found in the urine. In the jaundice due to poisoning by arseniuretted hydrogen, large amounts of bile acids were also sometimes met with in the urine.

We may now dismiss the subject of jaundice and the formation of bile pigments in the liver. We possess no positive knowledge as to the fate of the iron which, in the process that we have been discussing, must be detached from the hematin. In the liver we find very numerous compounds of iron, in which the iron is more or less firmly fixed; from very simple inorganic forms, such as oxid and phosphate of iron, and organic compounds in which it is more stable, to those in which the iron is as firmly bound as in hematin.[5] We know nothing as to the genetic connection of these compounds, which have scarcely been submitted to any inquiry.

As already mentioned, the FORMATION OF GLYCOGEN is one of the functions of the liver. The reasons why we are compelled

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[1] *Vide* Kunkel, *loc. cit.*, p. 463. Compare also Quincke, *loc. cit.*, p. 138.

[2] Minkowski and Naunyn, *loc. cit.*, p. 12.

[3] Heidenhain, in Hermann's "Handb. d. Physiol.," vol. v. part i. p. 268: Leipzig, Vogel, 1883.

[4] E. Stadelmann, *Arch. f. exp. Path. u. Pharm.*, vol. xiv. pp. 231, 422: 1881; vol. xv. p. 337: 1882; vol. xvi. pp. 118, 221: 1883. Compare also Afanassiew, *Zeitschr. f. klin. Med.*, vol. vi. p. 281: 1883.

[5] *Vide* St. Sz. Zaleski, *Zeitschr. f. physiol. Chem.*, vol. x. p. 453: 1886, where a full account of the literature on the relations of iron in the liver is given. Compare also the interesting illustrations of the microscopical preparations in the work of Minkowski and Naunyn, *loc. cit.*

to assume that the sugar which passes from the intestine into the portal blood is deposited in the liver as glycogen, have already been given (p. 188). Glycogen plays, in the metabolism of animals, a part similar to that which belongs to starch in the metabolism of plants: it is the form in which the excess of carbohydrates is stored up in the organism for future use.

Glycogen[1] is distinguished from starch by its property of swelling up and being apparently dissolved in cold water. The solution is however never clear, but opalescent and not diffusible. Glycogen therefore in this respect resembles the colloid gummy carbohydrates, dextrin, arabin, bassorin, and the like; but it is more complicated than dextrin, as this is obtained by the decomposition of glycogen. It yields products similar to those derived from starch when broken up, and is probably of as complex a nature.

There is no room for the storage of the whole excess of carbohydrates in the liver. The liver of mammals rarely yields as much as 10 per cent. of glycogen, and generally much less. The human liver therefore, which weighs 1500 grms., contains at most 150 grms. of glycogen. After a meal in which carbohydrates have been copiously consumed, much larger quantities often pass into the portal vein within a few hours, and we must bear in mind that at the commencement of a meal the liver contains some glycogen. It only becomes perfectly free from glycogen after several weeks' starvation. A large portion of the sugar, derived from the intestine, must therefore pass through the liver. But as the amount of sugar in the blood does not rise after a diet rich in that substance, the sugar must be deposited in other organs than the liver. We do, in fact, know that the muscles contain glycogen.[2] The percentage amount of this carbohydrate in the muscles is much

Cl. Bernard (*Gaz. méd. de Paris*, No. 13 : 1857; *Compt. rend.*, vol. xliv. p. 578: 1857) and V. Hensen (Virchow's *Arch.*, vol. xi. p. 395: 1857) each discovered glycogen independently of the other, and isolated it from the liver. Brücke (*Sitzungsber. d. Wien. Akad.*, vol. lxiii. part 2, p. 214: 1871) has shown a method for the quantitative estimate of glycogen. *Vide* also O. Nasse, Pflüger's *Arch.*, vol. xxiv. pp. 1–114: 1881: R. Böhm and Fr. A. Hofmann, *Arch. f. exper. Path. u. Pharm.*, vol. vii. p. 489: 1877; vol. viii. pp. 271, 375: 1878; vol. x. p. 12: 1879; Pflüger's *Arch.*, vol. xxiii. pp. 44, 205: 1880. Compare also Külz, Pflüger's *Arch.*, vol. xxiv. pp. 1–114: 1881, for a complete account of the literature on the subject.

[2] The occurrence of glycogen in the muscles was discovered by Bernard (*Compt. rend.*, vol. xlviii. p. 683: 1859) and by O. Nasse (Pflüger's *Arch.*, vol. ii. p. 97: 1869; and vol. xiv. p. 482: 1877). A summary of the first accounts of glycogen in muscle is given by E. Külz, *loc. cit.*, p. 42. Glycogen in small quantities is also present in other organs. Compare M. Abeles, *Centralbl. f. d. med. Wiss.*, p. 449: 1885.

smaller than that in the liver, and seems to vary in different animals; the muscles at the most contain 1 per cent., generally less than ½ per cent. Böhm[1] found the absolute quantity contained in the muscles of the cat nearly as large as that in the liver. The muscles of a horse, after nine days' starvation, still contained from 1 to 2.4 per cent. glycogen.[2] As we shall see directly, glycogen is the material of muscular work. It disappears entirely from the muscles and liver after fatigue and want of food;[3] and sooner from the liver than the muscles.[4] It may be taken as a fact that when there is an insufficient supply of food the organs which are at rest give up their store of glycogen to those that are working.

It is probable that glycogen is conveyed from one part of the system to another in the form of grape-sugar. When broken up by ferments, glycogen is converted, in the first instance, into a carbohydrate resembling dextrin, and into a variety of sugar resembling maltose.[5] But in the living body, the passage of the glycogen from the tissues into the blood causes a further advance in this change, and the glycogen is as completely converted into molecules of grape-sugar as it would be by boiling with dilute sulphuric acid. The majority of inquirers have been unable to show the presence of glycogen or of any colloid carbohydrates in the blood.[6]

Glycogen is not only a source of power for the muscles; it is likewise a source of heat. If we lower the temperature of a rabbit by cold baths and cold air, all but minute traces of the glycogen is found to have disappeared from the liver after a few hours.[7] Starvation deprives warm-blooded animals more rapidly of their glycogen than cold-blooded animals, and among

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[1] R. Böhm, Pflüger's *Arch.*, vol. xxiii. p. 51: 1880.

[2] G. Aldehoff (Külz's laboratory), *Zeitschr. f. Biolog.*, vol. xxv. p. 162: 1888.

[3] B. Luchsinger, "Experimentelle und kritische Beiträge zur Physiologie und Pathologie des Glycogens," *Vierteljahrschr. der Züricher naturforschenden Gesellschaft:* 1875. See also Pflüger's *Arch.*, vol. xviii. p. 472: 1878. G. Aldehoff, *Zeitschr. f. Biolog.*, vol. xxv. p. 137: 1889.

[4] Aldehoff, *loc. cit.*

[5] O. Nasse, Pflüger's *Arch.*, vol. xiv. p. 478: 1877: Musculus and von Mering, *Zeitschr. f. physiol. Chem.*, vol. ii. p. 413: 1878; E. Külz, *loc. cit.*, pp. 52–57 and 81–84.

[6] O. Nasse, "De materiis amylaceis, num in sanguine animalium inveniantur, disquisitio," Dissert.: Halle, 1866: Hoppe-Seyler. "Physiol. Chem.," p. 406: Berlin, 1881. Salomon comes to different conclusions (*Deutsche med. Wochenschr.*, No. 35: 1877). Frerichs ("Ueb. d. Diabetes," p. 6: Berlin, 1884) also comes to the conclusion that there is constantly a small amount of glycogen in the blood, for the most part contained in the white blood-corpuscles. This however is not a peculiarity of leucocytes, but is probably common to all cells.

[7] E. Külz, Pflüger's *Arch.*, vol. xxiv. p. 46: 1881. *Vide* also Böhm and Hoffmann, *Arch. f. exper. Path. u. Pharm.*, vol. viii. p. 295: 1878.

the former small animals with a relatively large surface lose it sooner than the bigger ones.[1] Starving rabbits lose their glycogen in from four to eight days; dogs not before two or three weeks; frogs, in summer, after from three to six weeks. Frogs which have had no food during the whole winter do not show an entire absence of glycogen until the spring. Hibernating mammals are equally slow in consuming their store of glycogen.[2]

If we introduce carbohydrates into the stomach, or directly into the blood of rabbits, whose liver, after six days of starvation, has been rendered quite free from glycogen, a large amount of glycogen is found in the liver after a few hours.[3]

It is probable that the glycogen stored in the liver and the muscles is not derived exclusively from the carbohydrates of the food. It appears that the albuminous and gelatinous substances of the food also take part in the formation of glycogen. Animals that have been exclusively fed for a considerable period on lean meat, exhibit large stores of glycogen in their liver and muscles. Naunyn[4] fed fowls for a long time (in one experiment for six weeks) exclusively on muscle, which had been stewed down and squeezed out, and therefore was almost entirely free from carbohydrates; and he then found large quantities of glycogen (as much as 3.5 per cent.) in the liver. Von Mering[5] fed a dog, which had been previously starved for twenty-one days, for four days exclusively on washed bullock's fibrin. The animal was killed six hours after it had been last fed, and the liver, which weighed 540 grms. contained 16.3 grm. of glycogen. A control animal of nearly the same size showed, after twenty-one days of starvation, 0.48 grm. of glycogen in the liver. It would necessitate very forced modes of explanation to assume from these and many other similar experiments that the glycogen did not arise from the proteid.

We may also quote, in support of the view that carbo-

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[1] B. Luchsinger, *loc. cit.*

[2] Schiff, "Unt. ueber die Zuckerbildung in der Leber," p. 30: Würzburg, 1859; Valentine, Moleschott's *Unters. zur Naturlehre*, &c., vol. iii. p. 223: 1857; C. Aeby, *Arch. f. exper. Path. u. Pharm.*, vol. iii. p. 184: 1875; Voit, *Zeitschr. f. Biolog.*, vol. xiv. p. 118: 1878.

[3] E. Külz, Pflüger's *Arch.*, vol. xxiv. pp. 1–19: 1881. The numerous experiments of a similar nature made by earlier authors are given here.

[4] B. Naunyn, *Arch. f. exper. Path. u. Pharm.*, vol. iii. p. 94: 1875.

[5] Von Mering, Pflüger's *Arch.*, vol. xiv. p. 282 : 1877. The experiments made on this subject by earlier authors are appended. *Vide* also Benj. Finn, *Verhandl. d. physik. med. Ges. zu Würzburg*, N.F., vol. xi. Heft i., ii.: 1876; and S. Wolffberg, *Zeitschr. f. Biolog.*, vol. xii. p. 310 (Exp. 4): 1876.

hydrates are formed from proteid, the fact that in the severe form of diabetes mellitus, under a protracted and exclusive flesh-diet, the secretion of sugar does not cease, and that the quantity of sugar increases in proportion to the amount of proteid consumed.[1]

Von Mering's experiments on phloridzin diabetes are well worth mentioning.[2] Phloridzin is a glucosid found in the root cortex of apple and cherry trees. If we administer a certain amount of this to a dog (1 grm. per kilo. body-weight) we find, after a few hours, sugar in the urine. This glycosuria ceases in two or three days, and we then find the liver and muscles totally free from glycogen. If we now give another dose of phloridzin, we again find a large amount of sugar excreted. Von Mering concludes that this must be derived from proteid. We must however acknowledge the possibility that this sugar may arise from fats. I have already (Lecture XIII.) noted certain fats which point to a conversion of fat into sugar, and would cite especially the constant percentage of sugar in the blood of starving animals which have long used up their store of glycogen, and sparing their proteid as much as possible, are living mainly at the expense of their fat. A conversion of fat into sugar has long been familiar to the vegetable physiologist. Certain seeds contain no starch, the place of this substance being taken by fat. If such seeds are allowed to germinate in the dark in order to prevent the formation of new organic substances, the fat is seen to disappear from the cotyledons and is replaced by starch, gum, sugar and cellulose.[3] If starchy seeds germinate in a glass tube over mercury no alteration occurs in the volume of the air in the tube. If oily seeds are placed under the same conditions, the mercury rises in the tube, since oxygen is used up in the transformation of fats into carbohydrates.[4] J. Seegen is of opinion that a similar conversion of fat into carbohydrate occurs in the liver of the mammal, and bases his argument on the following experiment. Pieces of liver from a freshly killed animal are weighed, cut up finely, and allowed to stand with defibrinated blood at the body temperature. To one

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[1] Von Mering, "Tageblatt der 49 Naturforscherversammlung in Hamburg," summarized in the *Deutsche Zeitschr. f. prakt. Med.*, No. 40: 1876; and No. 18: 1877; Külz, *Arch. f. exper. Path. u. Pharm.*, vol. vi. p. 140: 1876.

[2] Von Mering, *Verhandl. d. Congr. f. inn. Medicin.*, Fünfter Congress, Wiesbaden, p. 185: 1886; and Sechster Congress, Wiesbaden, p. 349: 1887.

[3] Sachs, *Botan. Zeit.*: 1859; Peters, "Landw. Versuchsstationen," vol. iii.: 1861.

[4] An experiment by Wiesner, described by Seegen in "Die Zuckerbildung im Thierkörper," &c., p. 155: Berlin, 1890.

portion of this mixture a fine emulsion of fat is added. Air is then allowed to bubble through the mixtures for five to six hours. At the end of this time the amount of sugar is determined in the mixtures, and is found to be always higher in the liver to which fat has been added. Seegen concludes that fat is converted in the liver into sugar. In harmony with this assumption is the fact that the blood of the hepatic veins is almost free from oxygen, whereas the blood flowing from other organs always contains considerable quantities of this gas.

We must conclude therefore that as soon as the amount of sugar in the blood sinks below normal, the liver pours into the blood sugar which may be derived not only from glycogen and proteid, but also from fats. Whether the other organs can also convert their fat into sugar, or whether the fat must be first transported to the liver in order to effect this conversion cannot as yet be determined.

Many attempts have been made to decide by experiment whether glycogen arises from the fatty materials of food. Almost all authors[1] agree that the glycogen of the liver does not increase in amount after fatty food.

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[1] A summary of these authors is given by Von Mering, Pflüger's *Arch.*, vol. xiv. p. 282: 1877.

LECTURE XXIII

THE SOURCE OF MUSCULAR ENERGY

In our last observations on the formation of glycogen and the behavior of carbohydrates in the body, I repeatedly stated that glycogen must be regarded as the material of muscular work. We will now proceed to consider the facts which have led to this view, and to give a connected account of all that is at present known concerning the source of muscular energy.

The most obvious theory that the source of muscular work is the metabolism of those substances which form the main constituents of muscle, viz., proteids, was obstinately maintained by Liebig[1] to the end of his life. This teaching was however shown to be erroneous by the following experiment:—

Fick and Wislicenus, from the Lake of Brienz,[2] ascended the Faulhorn, the summit of which is 1956 meters above the level of the lake. The urine excreted during the six hours' ascent and for the succeeding six hours was collected, and the nitrogen contained in it was estimated. During this time, and for twelve hours previous to the commencement of the experiment, only non-nitrogenous food, starch, fat, and sugar, had been taken. The consumption of proteid was calculated from the nitrogen found in the urine. In Fick it amounted to 38, and in Wislicenus to 37 grms. From the amount of heat produced by the combustion of the carbon and hydrogen in the proteid, a maximal value[3] was deduced for the heat-equivalent of the

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[1] It is very instructive to read the original works in which the reasons adduced in favor of and against Liebig's doctrine are given. To this end we recommend Liebig's treatise, "Ueber die Gährung und die Quelle der Muskelkraft und über Ernährung;" Liebig's *Ann. d. Chem. u. Pharm.*, vol. cliii. pp. 1 and 157; and Voit's reply, "Ueber die Entwickelung der Lehre von der Quelle der Muskelkraft und einiger Theile der Ernährung seit 25 Jahren," *Zeitschr. f. Biolog.*, vol. vi. p. 305: 1870. The older literature on this question is here critically treated.

[2] A. Fick and J. Wislicenus, *Vierteljahrschr. der Züricher naturforschenden Ges.*, vol. x. p. 317: 1865.

[3] That this value must be much too high is evident from what we have mentioned before (p. 61 *et seq.*).

proteid, and it was found that 37 grms. of proteid yielded 250 units of heat, which corresponds to 106,000 kilogrammeters of work. Wislicenus weighed 76 kgrms. It follows that, in merely raising his body to the summit of the mountain, he had done work amounting to $76 \times 1956 = 148,656$ kilogrammeters. But the work done during the ascent was really much greater; Fick and Wislicenus calculated that the work done by the heart and by respiration in the same time amounted to 30,000 kilogrammeters. We have also to consider that even on level ground every step entails work, which is converted into heat and is lost, and that the other parts of the body, the head and arms, are moved during the ascent, etc. It follows that much more work had been done than would be covered by the potential energy contained in the proteid consumed. The non-nitrogenous constituents of the food and of the body must therefore have been utilized as sources of energy.

The view that proteid is the exclusive working material of muscle is more precisely controverted by a series of very careful experiments on metabolism. These show that the excretion of nitrogen during twenty-four hours of extreme labor is as great as, or but little more than, the quantity excreted during rest; but that, on the other hand, the excretion of carbonic acid and the absorption of oxygen is much increased on the days of work, and that therefore during muscular work non-nitrogenous food is chiefly consumed.

Voit[1] was the first to carry out a careful experiment of this kind. He caused dogs to run in a large tread-mill. On the days before and after the day of work, the animals were quiescent with the same food. Some of the experiments were made on fasting animals. The output of nitrogen for twenty-four hours was accurately determined, and it resulted, from two experiments with fasting animals, that the excretion of nitrogen was not increased on the working days. In two other experiments with a fasting animal, and in two with a diet of lean meat, the increase was very slight.

More recently, O. Kellner[2] has instituted similar experiments on horses at the experimental farm of Hohenheim. On the working days, he found a greater increase in the excretion of nitrogen than was shown in the experiments of Voit. It was only when very large quantities of carbohydrates were given to the horses that this increase failed.

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[1] C. Voit, "Unt über den Einfluss des Kochsalzes, des Kaffees und der Muskelbewegungen auf den Stoffwechsel," p. 153, *et seq.:* München, 1860; and *Zeitschr. f. Biolog.*, vol. ii. p. 339: 1866.

[2] O. Kellner, *Landwirthshaftliche Jahrbücher*, vol. viii. p. 701: 1879; and vol. ix. p. 651: 1880.

Pettenkofer and Voit[1] have also made experiments on man to determine the influence of work upon the excretion of nitrogen. The elimination of carbonic acid, and indirectly the amount of oxygen consumed, was determined at the same time by the respiratory apparatus. They found that on the working days the excretion of nitrogen was identical with that on the days of rest, the food being the same. The amount of sulphuric and phosphoric acids secreted was not increased on the working days, but the excretion of carbonic acid and the absorption of oxygen rose very considerably.

Lavoisier[2] had already shown that the absorption of oxygen and the excretion of carbonic acid were increased by muscular work. Vierordt,[3] Scharling,[4] Ed. Smith,[5] C. Speck,[6] and others, using more perfect methods, have confirmed this discovery. The increase in the absorption of oxygen and in the excretion of carbonic acid has been determined not only by the investigation of the interchange of gases in the respiratory apparatus, but also by a comparative determination of the oxygen and the carbonic acid in venous blood, taken from the quiescent and the tetanized muscle. This was done by Ludwig and Sczelkow,[7] and finally in a masterly inquiry carried out in Ludwig's laboratory by Max von Frey,[8] with the advantage of all the improved technical aids.

From the experiments that have been quoted, it is apparent that muscle chiefly works with non-nitrogenous food, and carbohydrates readily suggest themselves, as they are invariably stored up in muscle in the form of glycogen. Cl. Bernard, the discoverer of glycogen, was also the first to observe that this store of glycogen disappears during work.[9] He also found that

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[1] Pettenkofer and Voit, *Zeitschr. f. Biolog.*, vol. ii. pp. 488–500: 1866. Compare also Felix Schenk, *Arch. f. exper. Path. u. Pharm.*, vol. ii. p. 21: 1874; and Oppenheim, Pflüger's *Arch.*, vol. xxiii. p. 484: 1880.

[2] Seguin and Lavoisier, "Premier mémoire sur la respiration des animaux," *Mem. de l'Acad. des Sciences*, p. 185: 1789; *Œuvres de Lavoisier*, Paris, Imprimerie impériale, vol. ii. pp. 688, 696: 1862; and Lavoisier's letter to Black, dated November 19, 1790, printed in the "Report of the Forty-first Meeting of the British Assoc. for the Adv. of Science," held at Edinburgh, in August, 1871, p. 191: London, 1872.

[3] Vierordt, "Physiologie des Athmens": Karlsruhe, 1845.

[4] Scharling, *Ann. d. Chem. u. Pharm.*, vol. xlv. p. 214: 1843: *Journ. f. prakt. Chem.*, vol. xlviii. p. 435: 1849.

[5] Ed. Smith, *Phil. Trans.*, vol. cxlix. (2) pp. 681, 715: 1859; *Medico-chirurg. Trans.*, vol. xlii. p. 91: 1859.

[6] C. Speck, *Schriften der Ges. zur Beförderung d. ges. Naturwissensch. zu Marburg*, vol. x.: 1871; *Arch. f. exper. Path. u. Pharm.*, vol. ii. p. 405: 1874.

[7] Ludwig and Sczelkow, *Wiener Sitzungsber.*, vol. xlv. p. 171: 1862; *Zeitschr. f. rat. Med.*, vol. xvii. p. 106: 1862.

[8] Max von Frey, Du Bois' *Arch.*, pp. 519, 533: 1885.

[9] Cl. Bernard, *Compt. rend.*, vol. xlviii. p. 683: 1859.

when a muscle is artificially brought to a state of quiescence by division of its nerve, its glycogen increases. These statements of Bernard have been subsequently confirmed by many experiments.[1] If one of the hind legs of a frog be tetanized, it is always found to contain less glycogen than the other, which has been at rest.

Külz[2] allowed dogs that had been previously well fed to starve for one day, and on this day to drag a heavy cart for from five to seven hours. The dog was then immediately killed, and the amount of glycogen in his liver determined. Of five dogs employed in this experiment, the liver in four showed that all but mere traces of glycogen had disappeared. The liver of the fifth, which was distinguished from the others by being old, very fat and sluggish, weighed 240 grms., and contained 0.8 grm. of glycogen. I have previously remarked that during starvation without work glycogen does not disappear from the liver of a dog until the third week (pp. 344–345).

Hence there can be no doubt that carbohydrates serve as a source of muscular energy.

However, it would be too much to assume that carbohydrates are the sole source of muscular energy. We have just become acquainted with experiments from which it appears very probable that glycogen is formed from proteid (p. 345). Hence we infer that proteid may also serve as a source of muscular energy. It is a fact that carnivora may be fed for a long time exclusively on lean meat, without impairing muscular vigor. I cannot conceive any explanation of the metabolism of the animals thus fed, without assuming that proteid may serve as a source of muscular power.

Nor is it improbable that fat may serve for the same purpose. It would not be difficult to determine this question by experiments upon fasting dogs. Külz has already shown that a fasting dog consumes its store of glycogen on the very first day of hard work. A determination of the excretion of nitrogen and carbon on subsequent days, when the work was continued, would afford a certain reply to the question whether chiefly proteid or chiefly fat supplies the animal with working power. When Voit made his experiments on fasting dogs, the animal generally worked only one day; in one of his experiments[3] however, the work was continued for three successive days, and they had been preceded by three fasting days with-

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[1] An account of these is given by E. Külz, Pflüger's *Arch.*, vol. xxiv. p. 42: 1881; and Ed. Marché, *Zeitschr. f. Biolog.*, vol. xxv. p. 163: 1889.

[2] E. Külz, *loc. cit.*, p. 45.

[3] Voit, "Ueb. d. Einfl. d. Kochsalzes," &c., pp. 157, 158.

out work. Külz's dogs worked and fasted for one day only, previous to which they had been supplied with ample food for some days, and still after the first day of work their glycogen had disappeared. It follows therefore that Voit's dog must have been quite free from glycogen on the second and third days of hunger and work. Nevertheless there was only a trifling increase in the excretion of urea. I think therefore it must be concluded from this experiment that the store of fat in this dog had been drawn upon to carry on its muscular work.

I hold that muscle draws its energy from all the three main classes of food-stuffs. We might assume *à priori*, on teleological grounds, that in the performance of its most important functions, the organism is to a certain extent independent of the quality of its food. As long as non-nitrogenous food is supplied in adequate quantity or is stored up in the tissues, muscular work is chiefly maintained from this store. When it is gone the proteids are attacked. The results obtained from the above-mentioned experiments of Kellner entirely agree with this statement; he found that, in the horse, the excretion of nitrogen is increased by muscular work only when the animal does not receive a sufficient supply of carbohydrates.

It has often been surmised that muscular energy is not derived from the processes of oxidation, but from those of decomposition. Certain facts seemed to favor this view. Thus Hermann[1] found that an excised muscle contains no removable oxygen, and that nevertheless it executes numerous contractions and gives off carbonic acid when placed in a medium deprived of all oxygen. We know that the chemical potential energy introduced by food may in part be converted, by mere breaking up without oxidation, into kinetic energy; that the heat of combustion of decomposition products is lower than that of the original food-stuffs, and that therefore heat must be liberated during decomposition. We have given direct proof that this development of heat accompanies many processes of decomposition. (Compare pp. 64, 153.)

The above-mentioned fact, that in muscular work the consumption of oxygen is increased, is not opposed to the assumption that only a part of the chemical potential energy is transmitted into kinetic energy during decomposition. The two processes, decomposition and oxidation, might occur at different periods; the former serves for muscular work, the

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[1] L. Hermann, "Unt. üb. d. Stoffwechsel der Muskeln, ausgehend vom Gaswechsel derselben": Berlin, 1867.

latter provides heat. Both processes might also be separated as to their locality, the decomposition occurring in the protoplasm of muscular fiber, while possibly the oxidation of the decomposition products occurs in other tissue-elements.

From this point of view the absorption of oxygen would mainly serve for the production of heat. There is a remarkable difference in animals in their requirement of oxygen, and it appears that the want is regulated by the amount of heat generated. A mammal requires at least from ten to twenty times as much oxygen, in proportion to its weight, as a cold-blooded animal. A bird uses up more than a mammal. A small animal, giving off more heat from a relatively larger surface, requires more than closely allied animals of a large size. Young animals require more than full-grown animals of the same species. These differences are well shown in the following table:

AMOUNT OF OXYGEN CONSUMED IN TWENTY-FOUR HOURS, IN PROPORTION TO 1 GRM. OF WEIGHT, IN C.CM. AT 0° C. AND 760 MM. HG.[1]

Sparrow	161.0
Duck	23.0 – 32.0
Dog	15.0 – 23.0
Man	7.0 – 11.0
Frog	1.0 – 2.0
Earthworm	1.7
Tench	1.3
Eel	0.97– 1.2
Lizard, hibernating	0.41

If it is correct to regard muscular energy as mainly produced by the decomposition of food, and heat chiefly by oxidation, we should expect that animals which develop no heat would require the smallest amount of oxygen. This is the case with the entozoa of warm-blooded animals, which reside in a uniformly high temperature. We know that the intestinal parasites live in a medium which is almost entirely free from oxygen, for the most recent and most careful analyses of intestinal gases have demonstrated no oxygen in them. We know that active processes of reduction occur in the intestinal contents; that they constantly give rise to nascent hydrogen; that sulphates are reduced to sulphids, and oxid to suboxid of iron. The amount of oxygen taken up by the intestinal parasites must therefore be excessively

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[1] The figures given for the consumption of oxygen in man are derived from the work of Pettenkofer and Voit (*Zeitschr. f. Biolog.*, vol. ii. pp. 486, 489 : 1866); those for fish from that of Jolyet and Regnard (*Arch. de Physiol. norm. et path.*, série ii. vol. iv. pp. 605, 608 : 1877). The remaining figures are from the work of Regnault and Reiset (*Ann. de Chim. et de Phys.*, vol. xxvi.: 1849).

small. It is possible that they attach themselves to the walls of the intestine and take up oxygen which is diffused from the tissues of the bowel, before it is taken possession of by the reducing substances of the intestinal contents. But it is also possible that mere traces of oxygen are sufficient for their wants, or even that they require no oxygen, as is asserted of certain bacteria and fungi (compare above, pp. 158, 244, note 3). This question can only be decided experimentally. I have made many experiments with the round worm (*Ascaris mystax*) of the cat, and have satisfied myself that these animals can live in media entirely free from oxygen for from four to five days, and be extremely active during the whole time.[1] Whoever has seen these movements must be convinced that oxidation is not the source of muscular energy in these animals.

The objection might be raised that they have a store of oxygen in their bodies, which is but loosely fixed. We must admit this possibility. Ascarides are sometimes found in the stomach. It is possible that they rise into the upper part of the digestive tract in order to supply themselves with oxygen. But this proceeding has no analogy with what is observed in higher animals; as soon as the supply of oxygen is cut off, the store contained in the oxyhemoglobin is consumed in a few minutes and the animals perish. Pflüger[2] and Aubert[3] have certainly shown that frogs may remain alive for several days in an atmosphere containing no oxygen, but only at a very low temperature, which causes a reduction of the entire metabolism of these animals to the lowest point.[4] If they are left at the temperature of the room, they become motionless after a few hours; while ascarides move about most actively at a temperature of 38° C. for several days in media devoid of all oxygen. I am far from applying to higher animals the conviction derived from the observation of these animals, that muscular energy is mainly due to processes of decomposition. Intestinal parasites, which are constantly surrounded by food-supplies, can afford to be wasteful of their potential energies, and only utilize that portion of them which is converted into kinetic energy by mere decomposition. Such a proceeding would be

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[1] G. Bunge, *Zeitschr. f. physiol. Chem.*, vol. viii. p. 48: 1883.

[2] Pflüger, in his *Arch.*, vol. x. p. 313: 1875.

[3] Aubert, *ibid.*, vol. xxiv. p. 293: 1881.

[4] As we might *à priori* expect, we find that in cold-blooded (*poikilothermic*) animals, a rise of the temperature of their environment causes increased metabolism and consumption of oxygen, whereas the reverse is the case in warm-blooded or *homoiothermic* animals. A critical account of the numerous experiments by which this statement has been established will be found in a paper by Voit, *Zeitschr. f. Biolog.*, vol. iv. p. 57: 1878. Compare also Max Rubner, Du Bois' *Arch.*, pp. 38, 248: 1885.

purposeless in the higher animals. I have already mentioned the reasons in favor of the view that in the higher animals oxygen penetrates through the capillary walls into the tissues (p. 244). With regard especially to muscular tissue, we have to add an important fact to the reasons adduced: the occurrence of hemoglobin in muscle.[1] Both probability and analogy justify the view that the hemoglobin performs the same functions in muscle as in blood, *i. e.*, that of oxygen-carrier.

The amount of kinetic energy, which may develop by mere decomposition without oxidation from the chemical potential energies of food, is much too small adequately to explain muscular work. Let us first consider the carbohydrates, which certainly are the chief source of muscular energy.

Unfortunately we are not sufficiently familiar with the nature of the process of decomposition of the carbohydrates in muscle. It has often been opined that they break up in the first instance into sarcolactic acid.[2] Normal blood invariably contains some lactic acid; the amount increases in tetanized animals, and when blood is artificially passed through a living and working muscle.[3] But it appears that the amount of lactic acid formed in muscle is too trifling to allow this process of decomposition to serve as a source of muscular energy. At any rate, we do not know how much of the carbohydrate in muscle undergoes this decomposition. We do not even know whether the lactic acid occurring in muscle is formed from the carbohydrates.[4] It is possible that during work there is not more lactic acid formed in the muscle than during rest, but that more is transmitted to the blood. Astaschewsky found less lactic acid in the tetanized than in the quiescent muscle.[5] The heat-equivalent of lactic acid has never been

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[1] W. Kühne, Virchow's *Arch.*, vol. xxxiii. p. 79: 1865; and Ray Lankester, Pflüger's *Arch.*, vol. iv. p. 315: 1871. These statements with regard to the occurrence of hemoglobin in muscle have been repeatedly doubted, but, as it appears to me, without adequate grounds. *Vide* St. Zaleski, *Centralbl. f. d. med. Wissensch.*, Nos. 5, 6: 1887. The earlier authors are here mentioned.

[2] Compare above, p. 312, note 2.

[3] *Vide* P. Spiro, *Zeitschr. f. physiol. Chem.*, vol. i. p. 111: 1877; Max von Frey, Du Bois' *Arch.*, p. 557: 1885; Gaglio, *ibid.*, p. 400: 1886; Wissokowitsch, *ibid.*, Suppl., p. 91: 1877; and M. Berlinerblau, *Arch. f. exper. Path. u. Pharm.*, vol. xxiii. p. 333: 1887.

[4] In favor of the view that lactic acid arises from the carbohydrate, Berlinerblau (*loc. cit.*) points out that when blood to which glucose or glycogen has been added, is artificially passed through the muscles, more lactic acid is formed than without them. Considerable quantities of lactic acid are formed in the dying muscle, but whence it arises is entirely unknown. Roehm has shown that it is not formed from glycogen (Pflüger's *Arch.*, vol. xxiii. p. 44: 1880).

[5] Astaschewsky, *Zeitschr. f. physiol. Chem.*, vol. iv. p. 397: 1880.

determined, so that we are unable to state how much kinetic energy is liberated during lactic fermentation.

Let us endeavor to represent to ourselves the amount of kinetic energy which may proceed from the decomposition of carbohydrates, by picturing to ourselves two processes in which the amount of kinetic energy liberated has been exactly determined: alcoholic fermentation and butyric acid fermentation. The amount of heat liberated during the latter process is larger than in the former, and we may assert that no greater amount of heat can be liberated in any of the various processes which sugar undergoes in decomposition. For of the three products resulting from butyric fermentation (butyric acid, carbonic acid, and hydrogen), only butyric acid can be further broken up, and but little heat can be liberated in this process. The breaking up of butyric acid into propane and carbonic acid is entirely analogous to the splitting up of acetic acid into methane and carbonic acid — a process in which we are equally unable to show a development of heat. Taking the numbers quoted at p. 62 as a foundation, I have calculated the combustion-heat of sugar and of its products of decomposition as follows:

	Calories, or metric heat-units.		Kgrms. muscular work.
1000 grms. of grape-sugar on complete combustion to CO_2 and H_2O, yield	3939	=	1,674,000
1000 grms. of grape-sugar, when split up into alcohol and CO_2, yield	372	=	158,100
1000 grms. of grape-sugar, when split up into butyric acid, CO_2, and H, yield	414	=	176,000
The amount of work done by Wislicenus in ascending the Faulhorn in six hours amounted to			148,656
The amount of work done by heart and respiration during the same ascent amounted to . . .			30,000

Accordingly we see that, had the work done during the ascent of the Faulhorn been carried out by the decomposition of carbohydrates, more than 1000 grms. of carbohydrates would have been required in six hours! This is out of the question. On the other hand, 100 grms. of sugar, if completely broken up and oxidized, would have sufficed to execute the work. This amount of carbohydrate is always stored up in our muscles, besides an equal quantity in the liver.

I think that my calculation proves that to perform their work our muscles not only utilize the kinetic energy liberated by the decomposition of the food, but that oxygen also penetrates the protoplasm of muscular fiber, and its affinity to the products of decomposition serves as a source of energy.

Here we may again refer to the question of the value of alcohol as a food. Even if we grant that alcohol is turned to account in the body as a source of energy, yet this store of energy is far smaller than that contained in the carbohydrate from which the alcohol was prepared. In the fermentation of a kilogram of sugar, as we have just seen, an amount of energy is wasted which would serve to carry a heavy man to the top of the Faulhorn. We must remember too that certain cells of our body can probably only avail themselves of the energy set free in the breaking down of food-stuffs, since no free oxygen ever reaches them (compare p. 341). We thus see how foolish it is for men to give the nourishing carbohydrates of the grape-juice and grain to be devoured by the yeast-fungus, while they themselves feast on the excreta of the fungus. Fruit berries, and milk too, are deprived of all their value in this way.

LECTURE XXIV

FORMATION OF FAT IN THE ANIMAL BODY

THE question regarding the origin of fat in the tissues of the animal body, a most important part of metabolism, remains for our consideration. Our views on this subject have undergone constant fluctuations and controversies during the last few decades; but we have arrived at the conviction, after many and careful experiments, that the fat in the tissues may be formed from all the three chief classes of organic food-stuffs, viz., from the fats, the proteids, and the carbohydrates.

From the comprehensive literature on the formation of fat,[1] I shall select those works which constitute the firmest basis of our present knowledge of this subject.

It was long doubted whether the fat of the tissues was derived from the FAT of the food; chiefly on the grounds that fat, being absolutely insoluble in water, could not as such penetrate the intestinal wall, and that it would previously have to be converted in the bowel into a soluble soap and soluble glycerin. The view that glycerin and fatty acids might again unite in the tissues on the other side of the intestinal wall was opposed by the belief that no syntheses could occur in the animal body. We have seen that both these objections have now been overcome; we know that all kinds of synthetic processes occur in the animal body, and that neutral fat does pass through the intestinal wall. Now, if fat globules permeate the tissues of the intestine, why may they not pass through the walls of the capillaries and through all the organs of our body? *À priori* therefore, there is nothing opposed to the view that the fat of our tissues is derived from the fat of our food. Franz Hofmann[2] was the first to give experimental proof that this is the case.

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[1] Voit supplies an interesting survey of the older literature on this subject. "Ueber die Fettbildung im Thierkörper," *Zeitschr. f. Biolog.*, vol. v. p. 79: 1869. Compare also "Ueber die Entwickelung der Lehre von der Quelle der Muskelkraft und einiger Theile der Ernährung seit 25 Jahren," *ibid.*, vol. vi. p. 371: 1870.

[2] Franz Hofmann, *Zeitschr. f. Biolog.*, vol. viii. p. 153: 1872.

Hofmann deprived a dog of all fat by starving him for thirty days. We are able to determine the exact period when all the fat that is stored in the tissues is consumed. We have already seen that a starving animal at first lives mainly upon its store of glycogen, and subsequently upon its fat. It uses the greatest economy with regard to its proteid. That very little of the latter is decomposed is shown by the minute excretion of nitrogen, which at first falls, and then remains almost permanently the same. It is only after a longer period, which may vary from the fourth to the fifth week according to the original amount of fat, that a sudden rapid increase takes place in the excretion of nitrogen. This is the period at which the store of fat is used up, and when the animal commences to depend exclusively upon its store of proteid. The animal will now speedily perish. If the animal is killed at the time when the sudden increase of the nitrogenous excretion occurs, all the organs and tissues are found to be deprived of fat. If it is killed earlier a certain amount of fat is still found.[1]

Armed with this knowledge, Hofmann was able to determine when his starving dog was free from all fat. He now fed him on a diet containing a great deal of fat and but little proteid, viz., bacon and a small quantity of meat. The amount of proteid and fat in the food had been accurately estimated. After five days the animal was killed, and the amount of fat and proteid remaining in the intestine, as well as the fat in the whole body, was measured. It was found that during the five days the dog had absorbed 1854 grms. of fat and 254 grms. of proteid, and had deposited 1353 grms. of fat in his body. This large amount of fat could not have arisen from the proteid. It follows therefore that the fat of the food had been deposited in the tissues.

Pettenkofer and Voit[2] obtained the same result by a different method. They fed dogs with fat and a little meat, and by the use of the respiratory apparatus they measured the total income and output. Their experiments showed that all the nitrogen consumed was reëxcreted, but not all the carbon. A very large proportion of the carbon was retained. It was to be inferred that a non-nitrogenous compound had been stored in the tissues, and this could be nothing but fat, because there is no other non-nitrogenous compound which

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[1] When the fasting animal, at the commencement of the experiment, is unusually fat, it may happen that it dies from failure of its proteids even before the supply of fat is consumed.

[2] Pettenkofer and Voit, *Zeitschr. f. Biolog.*, vol. ix. p. 1: 1873.

is met with in the tissues in such large quantities. The fat deposited in the tissues could not be due to the decomposed proteid, as its amount was proportionately too large. It was possible to calculate with precision how much proteid had been decomposed by the quantity of nitrogen excreted. The maximum amount of fat formed from the decomposed proteid could be calculated on the assumption that the nitrogen had been separated from the proteid molecule as urea. The amount of fat resulting from this calculation was much less than that actually found in the body; it was therefore evident that this must be derived from the fat of the food.

We must now inquire whether it is only that portion of the fat of food which is absorbed unaltered as a neutral glycerid that can be stored up in the tissues, or whether that part which is split up in the intestine (compare pp. 164–166) can also be regenerated and assimilated.

Munk[1] has recently performed the most careful investigations to determine this question. He showed, in the first instance, that free fatty acids are absorbed from the intestine in large quantities as neutral fats. If free fatty acids are shaken up with a dilute solution of alkaline salts, a small portion of the fatty acids is saponified, the remainder is emulsified; the same takes place in the intestine. Dogs, after the consumption of a large quantity of free fatty acids, exhibited only a very small portion in their feces, but their chyle-ducts were full of a white emulsion.

The same inquirer also proved that free fatty acids exercise the same economizing effect upon proteids as neutral fats. A carnivorous animal, in order to maintain its body weight, requires nearly one-twentieth of this weight daily of lean meat.[2] A dog weighing 25 kgrms. consequently requires 1200 grms. of meat. If we give him less, he excretes more nitrogen than he consumes, and he feeds upon the proteids of his tissues. But if we add fat to the meat of his food, the dog, although consuming less meat, maintains his nitrogenous equilibrium.[3] Munk established the nitrogenous equilibrium in a dog weighing 25 kgrms. with 800 grms. of meat and 70 grms. of fat, and then showed that this equilibrium remained the same if, instead of the 70 grms. of fat,

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[1] Immanuel Munk, Du Bois' *Arch. f. Physiol.*, p. 371: 1879; and p. 273: 1883; Virchow's *Arch.*, vol. lxxx. p. 10: 1880; and vol. xcv. p. 407: 1884. The earlier literature is here quoted.

[2] Bidder and Schmidt, "Die Verdauungssäfte und der Stoffwechsel," p. 333: Mitau and Leipzig, 1852; Pettenkofer and Voit, *Ann. d. Chem. u. Pharm.*, Suppl., ii. p. 361: 1862.

[3] Munk, Virchow's *Arch.*, vol. lxxx. p. 17: 1880.

he gave the dog, with the same amount of meat, the free fatty acids obtained from the 70 grms. of fat. In a second experiment, the nitrogenous equilibrium was produced in a dog weighing 31 kgrms. with 600 grms. of meat and 100 grms. of fat, and this was maintained when subsequently the free fatty acids of 100 grms. of fat were given him with the same amount of meat for three weeks.

The important fact has further been determined by Munk[1] that, after feeding with free fatty acids, only a very small quantity of fatty acids and soaps, but much neutral fat, was contained in the chyle. He fed dogs with meat and fatty acids, and introduced a cannula into the thoracic duct; a few hours later, he determined the amount of chyle flowing out, and the quantity of neutral fat, fatty acids, and saponified matter contained in it. He found that, in the same time, from ten to twenty times more neutral fat passes through the thoracic duct than during the digestion of pure proteids, while the amount of soaps remains unaltered. The proportion of the free fatty acids generally reached only to between one-twentieth and one-tenth, in one case less than one-thirtieth, of the neutral fats. It follows that a synthesis of fatty acids with glycerin takes place during the passage from the intestinal surface to the thoracic duct.[2] We have no precise information as to the locality where this synthesis is effected. It may be in the epithelial cells, in the adenoid tissue of the intestine, or in the lymphatic glands of the mesentery. A preliminary communication made by Ewald[3] shows that this synthesis also occurs in the intestinal mucous membrane after it has been excised.

We do not know the source from which the glycerin arises that is necessary for this synthetic process. At all events, Munk's experiment proves that the glycerin in the fat of our body need not always be derived from the fat of our food; it may possibly result from the breaking up of the proteids and carbohydrates.

We must confess that the fate of the glycerin in our body is entirely unknown to us, and at present we are unable to say what becomes of the glycerin which is separated in the

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[1] Munk, Virchow's *Arch.*, vol. lxxx. p. 28, *et seq.:* 1880.

[2] O. Minkowski (*Arch. f. exper. Path. u. Pharm.*, vol. xxi. p. 373: 1886) arrived at the same result. He had the opportunity of experimenting on a patient suffering from extreme ascites, the result of a rupture of a chyle-vessel. A large quantity of chyle was obtained by puncture. After administering to this patient free erucic acid, the neutral glycerid of this acid was detected in the chyle.

[3] C. A. Ewald, Du Bois' *Arch.*, p. 302: 1883.

intestine from the fat. If a large quantity of glycerin is introduced into the stomach of a man or a dog, diarrhea occurs, and of the glycerin that is absorbed a portion passes unaltered into the urine.[1] Smaller quantities do not produce such consequences; in the dog, the proportion ought not to exceed 1.5 grm. to 1 kgrm. of weight.

Finally, Munk has given definite proof that the fat synthetically formed is also stored up in the tissues of the body.[2] A dog weighing 16 kgrms. was rendered almost devoid of fat by starvation for nineteen days, during which time he lost 32 per cent. of his original weight. In the course of the next fourteen days the dog consumed 3200 grms. of meat, and 2850 grms. of fatty acids prepared from mutton fat. With this diet, its weight rose again by 17 per cent. The animal was now killed, and showed an enormously developed panniculus adiposus; there was a copious deposit of fat in the intestines, and a well-marked fatty liver. The deposit of fat removed by scalpel and scissors yielded nearly 1100 grms. of fat that was solid at the temperature of the room, and only melted at a temperature of 40° C. while normal dog's fat is semi-fluid at 20°. It follows that the fatty acids which had been introduced were deposited after combining with glycerin that had formed in the body. If the deposit of fat be attributed to an economizing influence, exercised by the fatty acids introduced, and all the fat deposit be regarded as entirely originating from the proteid, it is not intelligible why mutton fat was deposited instead of normal dog's fat.

In a second experiment,[3] Munk fed a dog, which had been deprived of fat by starvation, with colza oil. In this case four-fifths of the fat deposited in the organs were liquid at the temperature of the room; when warmed to 23°, the whole of it melted; and at 14° a granular crystalline sediment formed. This fat contained 82.4 per cent. of oleic acid, and 12.5 per cent. of fixed acids; whereas normal dog's fat yields on an average only 65.8 per cent. of oleic and 28.8 per cent. of solid acids. In addition to this, erucic acid ($C_{22}H_{42}O_2$), which is an ingredient of colza oil but absent from animal fat, was proved to be present.

Previous to Munk, two similar experiments had been

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[1] B. Luchsinger, "Experimentelle und kritische Beiträge zur Physiologie und Pathologie des Glycogens." Inaug. Dissert., p. 38, *et seq.:* Zurich, 1875; Munk, Virchow's *Arch.*, vol. lxxx. p. 39, *et seq.:* 1880; Arnschink, *Zeitschr. f. Biolog.*, vol. xxiii. p. 413: 1887.

[2] J. Munk, Du Bois' *Arch.*, p. 273: 1883.

[3] J. Munk, Virchow's *Arch.*, vol. xcv. p. 407: 1884.

carried out by Lebedeff[1] with the same result in two dogs, one of which had been fed with linseed oil, the other with mutton fat. The fat in the tissues of the former did not congeal at 0°, the fat of the latter had a melting-point at above 50°.

All these experiments prove conclusively that the fat of food is absorbed and deposited unchanged.

We will now consider the second point as to whether fat is formed from PROTEID in the animal body. As fat takes the place of proteid in the cells and fibers in cases of fatty degeneration, we should suppose that fat necessarily proceeds from this source. But this fact cannot be interpreted as absolute proof of the origin of fat from proteid. We must not forget that in the living body there is a constant nutritive interchange going on directly or indirectly between all the tissue-elements. It is possible that in cases of fatty degeneration the proteids or their decomposition-products may pass away from the degenerating tissues, and be replaced by fat or its components from other tissues.

An exact quantitative examination of the total metabolism during a process of fatty degeneration, such as occurs in phosphorus-poisoning in which all parts of the body are rapidly involved, would show whether fat arose from proteid or not. The most careful investigation of this process was carried out in Voit's laboratory at Munich by J. Bauer.[2] He estimated the output of nitrogen and carbonic acid and the income of oxygen in fasting dogs. He then poisoned them with phosphorus, which was either given them by mouth in small doses spread over several days, or subcutaneously injected dissolved in oil. The consequence was that double the amount of nitrogen was eliminated,[3] and that the amount of carbonic acid excreted and of oxygen absorbed, dropped to one-half. The nitrogen from a large amount of proteid therefore was split off with a small quantity of carbon by the action of the phosphorus; a remnant free from nitrogen remained unconsumed in the body. If the animals died a few days after the administration of phosphorus, a post-mortem examination

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[1] A. Lebedeff (Salkowski's laboratory in Berlin), *Med. Centralbl.*, No. 8: 1882.

[2] Jos. Bauer, *Zeitschr. f. Biolog.*, vol. vii. p. 63: 1871; and vol. xiv. p. 527: 1878.

[3] The increase in the excretion of nitrogen after phosphorus-poisoning was shown before Bauer by O. Storch, "Den acute Phosphorforgiftning," &c., Dissert.: Kjobenhavn, 1865. Paul Cazeneuve has confirmed Storch's and Bauer's results in the *Revue mensuelle de Médec. et de Chirurg.*, vol. iv. pp. 265, 444: 1880.

showed all the organs to be in a state of fatty degeneration. In one case, the dried muscles contained 42.4 per cent., the dried liver 30 per cent. of fat, whereas only 16.7 per cent. was found in normal dried dog's muscle and only 10.4 per cent. in normal dried liver. Fat was therefore formed from proteid in phosphorus-poisoning. It cannot be objected that the fat had passed in from the fatty connective tissue in the muscles and in the liver, because the dog had been starved for twelve days before the commencement of the poisoning, and died on the twentieth day of starvation. But experience has shown that in dogs all fat visible to the naked eye disappears from the subcutaneous cellular tissue and the mesentery after twelve days of starvation.

Arsenic and antimony, which are chemically so closely related to phosphorus, seem to operate in a similar manner. They need not however be administered as free elements, as they also, when in the oxidized condition, cause increased elimination of nitrogen and fatty degeneration of the organs.[1] We are at present unable even to suggest an explanation of this action.

The experiments with phosphorus-poisoning only prove the origin of fat from proteid under these definite abnormal conditions. The question is whether this conversion likewise takes place under normal circumstances.

The following simple experiment made by Franz Hofmann[2] on fly-maggots, undoubtedly proves that fat does arise from proteid under normal conditions. It is an easy matter to collect, free from impurity, the eggs of the *Muscida vomitoria*, which are laid in heaps on a corpse in the summer-time. Part of the eggs so obtained was employed by Hofmann to estimate the amount of fat; the other part was allowed to develop on blood. The fat in the blood was also determined. After the maggots were full-grown, the fat in them was likewise ascertained. It was found that there was ten times as much fat in the full-grown maggots as in the eggs and blood together. For instance, in one experiment, 0.02 grm. of eggs containing 0.001 grm. of fat developed in 52 grms. of blood, which had 0.017 grm. of fat, the full-grown maggots containing 0.201 grm. of fat. This can only have been formed from the proteid of the blood; it cannot be referred to the sugar of

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[1] Gähtgens, *Centralbl. f. d. med. Wissensch.*, p. 529: 1875; Kossel, *Arch. f. exper. Path. u. Pharm.*, vol. v. p. 128: 1876; Gähtgens, *ibid.*, vol. v. p. 833: 1876; and *Centralbl. f. d. med. Wissench.*, p. 321: 1876; and Salkowsky, Virchow's *Arch.*, vol. xxxiv. p. 73: 1865.

[2] Franz Hofmann, *Zeitschr. f. Biolog.*, vol. viii. p. 159: 1872.

the blood, for 50 grms. of blood seldom contains more than 0.07 grm. of sugar, and even this far too small a quantity must have decomposed very rapidly; besides, the maggots had not consumed nearly all the blood.

From the following experiments on dogs, Pettenkofer and Voit[1] came to the conclusion that fat may be formed from proteid in mammals with a normal dietary. They fed them on large quantities of lean meat, and with the help of the respiratory apparatus they determined the total income and output. It was found that all the nitrogen, but not all the carbon, of the meat reappeared in the excretions. In one experiment,[2] for instance, in which a dog of 34 kgrms. weight ate 2800 grms. of meat, the whole of the nitrogen was eliminated, against only 271 grms. of the carbon, of which 313 grms. had been taken; 42 grms. were therefore missing. These remained behind in the body as a non-nitrogenous compound, and moreover, as Pettenkofer and Voit concluded, in the form of fat. It may be objected that this compound may have been glycogen just as well as fat. The amount of glycogen stored in the body of the carnivora is by no means inconsiderable, and varies widely. Böhm and Hofmann[3] found it amounted from 1.5 to 8.5 grms. per kilogramme of a cat's weight. The 42 grms. of carbon correspond to about 100 grms. of carbohydrates. If therefore we assume that the former are stored in this form, there must be an increase of glycogen amounting to 3 grms. per kilogramme of the body-weight, which does not appear impossible. But we ought not to forget that this increase of glycogen must take place in one day; the animal had had the same food on the previous day, therefore so great a change in the amount of glycogen was not very probable. But the experiments must be continued over a longer time before this point can be definitely settled. It might however be decided in another way, *i. e.*, if it were possible to make an exact comparison of the income and output of oxygen. The difference in the amount of oxygen in fat and glycogen is very considerable. It must therefore be possible to determine the form in which carbon is stored up from the quantity of the oxygen remaining in the body. But at present we have no method of directly estimating the amount of oxygen in food, and even the in-

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[1] Pettenkofer and Voit, Liebig's *Annal.*, Suppl. ii. p. 361: 1862; *Zeitschr. f. Biolog.*, vol. vi. p. 377: 1870; and vol. vii. p. 433: 1871.

[2] *Ibid.*, vol. vii. p. 487: 1871.

[3] Böhm and Hofmann, *Arch. f. exper. Path. u. Pharm.*, vol. viii. p. 290: 1878.

spired oxygen is calculated, according to Pettenkofer's method, from the difference.

One more objection may be raised to the experiment made by Pettenkofer and Voit, *i. e.*, that the meat was not quite free from fat and carbohydrates. The formation of fat from proteid in the organism of the mammal under normal conditions has therefore not yet been decisively proved.[1] But it is however highly probable, because it is certainly the case with the lower animals under normal circumstances, and with mammals under pathological conditions. Moreover, it may be adduced in favor of the normal formation of fat from proteid that, as we have already seen (p. 345), glycogen owes its origin to proteid, and fat to glycogen, and in fact to any carbohydrates, as will be shown directly. No chemical explanation of the formation of fat from proteid can at present be offered. However, the process must not be regarded as of so simple a nature that the fat is immediately split off from the gigantic proteid-molecule as a preformed radical. Profound decompositions, metamorphoses, and consequent syntheses are going on, of which we cannot at present form even a conception.

We now come to the third and last point, as to whether the CARBOHYDRATES are converted into fat in the animal body. From the numerous experiments made on this subject, we will select the following, as being perfectly reliable in their results.

N. Tschervinsky[2] made his experiments with young pigs. In one he used two of ten weeks old from the same litter, No. 1 weighing 7300 grms., and No. 2 7290 grms. It would therefore be supposed that each had about the same proportion of fat and proteid as the other. No. 1 was killed, and all the fat in the body was estimated, as well as the nitrogen, from which the maximum of proteid was determined. No. 2 was then fed on barley for four months. The barley was analyzed, and an account was kept of the barley consumed. The amount of undigested fat and proteid was also estimated by analysis of the excretions; and in this way, the quantity of

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[1] The remaining experiments quoted in favor of the view that fat is formed from proteid are likewise inconclusive. Compare Subbotin, Virchow's *Arch.*, vol. xxxvi. p. 561: 1866; and Kemmerich, *Centralbl. f. d. med. Wissensch.*, p. 465: 1866; and p. 127: 1867. Compare also Pflüger's criticism of Voit's experiments, Pflüger's *Arch.*, vol. li. pp. 229 and 317: 1891.

[2] N. Tschervinsky, *Landw. Versuchsstationen*, vol. xxix. p. 317: 1883. Experiments of a similar character by other authors led to the same results (F. Soxhlet, *Zeitschr. d. landwirthschaftlichen Vereins in Bayern*, August-Heft, 1881; B. Schulze, *Landw. Jahrb.*, 1, 57: 1882; St. Chaniewski, *Zeitschr. f. Biolog.*, vol. xx. p. 179: 1884).

these two substances absorbed by the animal in the four months was ascertained. The animal, whose weight had increased to 24 kgrms., was now killed, and the proportion of proteid and fat in the whole body determined.

No. 2 contained	2.52	kgrms.	proteid,	and	9.25	kgrms.	fat.
No. 1 "	0.96	"	"	"	0.69	"	"
Thus there were added .	1.56	"	"	"	8.56	"	"
Taken up with the food .	7.49	"	"	"	0.66	"	"
Difference . . .	—5.93				+7.9		

Thus 7.9 kgrms. of fat had been added in the body — an amount which could not have originated from the fat of the food; of this only the smallest portion could have arisen from the 5.93 of the proteid that was derived from the food, and was not deposited in the form of proteid. At least 5 kgrms. of fat must therefore owe its origin to the carbohydrates of the diet. This is so large a proportion as to refute all doubts, and particularly the objection that the identity in the amount of fat and proteid in both animals, upon which the whole experiment rests, as an arbitrary assumption.

A different method was adopted by Meissl and Strohmer.[1] They fed a one-year-old Yorkshire pig (a good fattening breed), weighing 140 kgrms., for seven days upon rice, which is poor in fat and proteids and rich in carbohydrates. Two kgrms. were administered to the animal every day. The rice had been analyzed; the urine and feces were collected and also analyzed. On the third and sixth days of the experiment the animal was placed in Pettenkofer's respiratory apparatus, in order to determine the excretion of carbonic acid. The result was that 289 grms. of the carbon daily ingested, and 6 grms. of the nitrogen, were retained in the body: 38 grms. of proteid with 20 grms. of carbon correspond to the 6 grms. of nitrogen. It follows that 269 grms. of carbon must have been daily retained in the body as fat. It is impossible that so large a quantity of carbon could every day have been stored up as glycogen. How then was this quantity of fat formed? Of the daily food, 5.3 grms. of fat and 104 grms. of proteid had been digested; of the latter, 38 grms. had been deposited. The remaining 66 grms. of proteid and the 5.3 grms. of fat cannot have yielded the 269 grms. of carbon

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[1] E. Meissl and F. Strohmer, *Sitzungsber. d. k. Akad. d. Wissensch. in Wien.*, vol. lxxxviii., Abth. III., Juli-Heft, 1883.

necessary for the deposit of fat, which must therefore be derived from the carbohydrates.

It has often been asserted that the formation of fat from carbohydrates takes place only in herbivora and omnivora, and not in carnivora. I therefore briefly mention the following experiment, which Rubner,[1] with the help of a respiratory apparatus, made on a dog. The animal, after fasting two days, was fed on cane-sugar and starch. A large quantity of carbon was retained — much too large, in fact, to be accounted for by the deposit of glycogen; it follows that fat had been formed from carbohydrates.

The formation of fat from carbohydrates offers a complete enigma to the chemist, and, more than anything else, proves that the synthetic processes occurring in the animal cell are as complicated as those in the vegetable cell.

Many attempts have been made to utilize our knowledge with regard to the formation of fat, in order to determine the causes of corpulency in man, and the means of counteracting and preventing it. The error has been committed of attributing the cause of obesity to too ample a diet, or even to an unsuitable combination of food, such as a diet with an excessive proportion of carbohydrates or of fat.

It is both right and natural for a man to eat whatever he likes and as much as he likes, and, if he otherwise leads a healthy life, this system does not conduce to corpulency. Why should we accuse a normal function of being the cause of a pathological process? Obesity is in all cases due to insufficient employment of the muscles. A person taking bodily exercise does not become fat, whatever form of diet he adopts. I quite admit that the tendency to corpulency may vary considerably in different people; but this only shows that the organs which constitute half the weight of the body may not be suffered to become atrophied with impunity in every case. There is no such thing as a disposition to stoutness which may not be overcome by muscular work. Show me a single fat field-laborer! It cannot be said that all these people are badly fed; many of them are as well nourished as it is possible to be, and their diet is certainly never poor in carbohydrates, nor often in fatty matter.

It is well known that the deposit of fat is encouraged by the use of alcohol, for which we are at present unable to give a satisfactory explanation. It readily suggests itself that alcohol, as a very combustible substance, exercises an economizing effect upon organic articles of diet, which are all capable of

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[1] Max Rubner, *Zeitschr. f. Biolog.*, vol. xxii. p. 272: 1886.

being converted into fat. But it is possible that alcohol promotes the formation of fat, in the same way as we have seen with other poisons, such as phosphorus, arsenic, and antimony (*vide supra,* pp. 120–121 and 363–364). In a great measure, the influence of alcohol on fat-formation may be attributed to the paralyzing influence it exerts upon the human brain, causing indolence and indisposition to bodily exertion. The therapeutics of corpulency are therefore very simple: the patient must be prohibited the use of all alcoholic beverages, and he must be required to take exercise. In many cases, to forbid alcohol is all that is required. If the heart however already shows signs of weakness and fatty degeneration, it is necessary to be cautious in ordering muscular exercise, and not to advise sudden and violent exertion. Corpulency should not be met by a so-called short cure, such as mountaineering during a few weeks in the year. The cure should last as long as life, and should merely consist in putting the muscles to their natural use. That however is the very thing the wealthy patient will not do, any more than he will renounce his alcohol. Physicians therefore have devised the most extraordinary methods for reducing fat, by which possibly some thousands have been cured to death. The absurdity of all these cures consists in trying to substitute one abnormality for another. The physician endeavors to compensate for insufficient muscular work by insufficient nourishment, or by a badly composed diet, or even by causing an imperfect digestion of the food (through administering saline purgatives); in other cases, he permits the continued use of alcohol while withdrawing the carbohydrates and fats.

If the first irregularity be entirely and permanently overcome, it is unnecessary to interfere in any other way with the natural course of the vital functions.

LECTURE XXV

IRON

The amount of iron contained in the adult human body is not accurately known. We can only estimate it approximately from the quantities which I have found in the total organism of small mammals.

A mouse contains	100 mg. Fe	per kilo. body-weight.
A guinea-pig "	52 " "	
A rabbit "	46 " "	

It thus appears that animals are relatively poorer in iron as the body-weight increases, and that we must therefore reckon not more than 46 mg. Fe per kilo. in man. The amount of iron in a body weighing 70 kilos, would therefore be 3.2 gr., and this is a maximum value. A minimal estimate may be computed from the amount of iron in the blood. According to Bischoff, our body contains 7.1–7.7 per cent. blood, and in the blood, according to C. Schmidt, the iron amounts to 0.049–0.051 per cent. Hence the iron in the blood of a man weighing 70 kilos, may be reckoned at something between 2.4–2.7 gr. and therefore the total amount in the body must be between 3.2 and 2.4. This iron is chiefly contained in the hemoglobin of our blood. We have therefore to inquire: From what is the hemoglobin formed? It does not exist in the food of most vertebrates, except in the case of those carnivora and omnivora which live upon other vertebrates. Among the invertebrates there are only a very few which contain a small quantity of hemoglobin in certain tissues. The majority of the vertebrates must therefore form their hemoglobin from other compounds of iron, the nature of which we will now consider.

Until recently little investigation has been made on this subject. As oxid of iron was found in the ash of all articles of diet, it was assumed that hemoglobin, which is well known to be a compound proteid, was formed by synthesis from oxid of iron and proteid.

It is difficult to understand how such a theory could have been universally adopted at a time when Liebig's doctrine of the universal antithesis in the metabolism of plants and animals prevailed. As is well known, Liebig had taught that synthetic changes could only be carried out in plants, the animal body being able to effect only disintegrative changes. It is true that this theory was shortly afterwards overthrown by Köhler's discovery of the synthesis of hippuric acid in the animal body. But hippuric acid is relatively a very simple compound; it contains only 9 atoms of carbon in the molecule, whereas hemoglobin has at least 700. It is therefore inconceivable how anyone could ever imagine that such a complex compound could be produced in our body; that moreover the inorganic iron should combine with its 32 atoms of carbon to form so stable a compound as hematin, which is united with proteid in the hemoglobin molecule. The iron cannot be separated from the hematin even with the strongest reagents. It cannot be detected in the hematin by means of ammonium sulphid; it is not split off on boiling with alkalies or most acids.

The universal acceptance of this doctrine concerning the synthesis of hemoglobin from oxid of iron and proteid would be quite incomprehensible were it not for the success which physicians think they have achieved in the treatment of chlorosis by the administration of inorganic preparations of iron. In chlorosis the amount of hemoglobin in the body is diminished; after iron salts have been taken it is increased. Hemoglobin is an iron compound. What could be more natural than the conclusion that the iron administered was used to form the hemoglobin? Nevertheless this conclusion seems to have been erroneous.

Later investigation has shown that the iron given by physicians in chlorosis, with the object of making hemoglobin from it, is probably not absorbed at all.

So far as I am aware, the first experiments which threw a doubt upon the absorbability of preparations of iron were published by Vincenz Kletzinsky[1] in 1854. His communication however is short and lacking in precision; the figures appear so little trustworthy that no notice was taken of the work. It was quite unknown to me at the time that I undertook my experiments on iron. Kletzinsky found that, in seven experiments on himself, metallic iron, oxid of iron, sulphid of iron, iodid of iron, acetate, lactate, and malate of iron could be recovered without loss from the feces. The same result

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[1] V. Kletzinsky, *Zeitschr. d. k. k. Gesellsch. d. Aerzte z. Wien.*, Jahrgang 10, vol. ii. pp. 281–289: 1854.

was obtained from careful experiments carried out by E. W. Hamburger[1] with ferrous sulphate on the dog, and by Marfori[2] in Schmiedeberg's laboratory with lactate of iron on the same animal.

The inorganic preparation of iron administered by the mouth does not enter into the urine, which in a normal state contains an inappreciable quantity of this substance. In experiments on animals in which inorganic compounds of iron were given internally, the amount of iron in the urine rose slightly only if the doses were so large or were continued so long as to render it probable that the intestinal epithelium was inflamed.[3]

We might conclude from these researches that inorganic preparations of iron are not absorbed from the normal intestine. But there is still an objection which must be refuted, viz., the possibility that the iron taken may be absorbed, but may be again excreted in the intestine. This objection has the more weight owing to the fact that the iron absorbed from the food and set free in the normal process of metabolism takes this path. This may be seen in fasting animals. The iron which appears in the feces of fasting animals cannot come from unabsorbed iron, but must have been excreted into the intestine. Bidder and Schmidt[4] found 6 to 10 times more iron in the feces than in the urine of fasting cats. The same result was obtained in recent experiments on the metabolism of fasting men; 7 to 8 mg. iron were found daily in the feces.[5]

As regards the path by which the iron reaches the intestine, we can only say with certainty that it is not by way of the bile, since the latter contains almost unweighable amounts of this substance. It is therefore probable that the main bulk of the iron is eliminated through the intestinal wall. The justice of this assumption is most clearly shown by an experiment of Fritz Voit.[6] In the dog he isolated a length of small intestine

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[1] E. W. Hamburger, *Zeitschr. f. physiol. Chem.*, vol. ii. p. 191: 1878.

[2] Pio Marfori, *Arch. f. exper. Path. u. Pharm.*, vol. xxix. p. 212: 1892.

[3] In many of the most recent experiments on the administration of inorganic forms of iron, this substance has been found in larger quantities in the intestinal wall, in the liver, in the chyle, &c. But in all these cases the small animals were given too large amounts of iron in proportion to their body-weight. *Vide* H. W. F. C. Woltering, *Zeitschr. f. physiol. Chem.*, vol. xxi. p. 186: 1895; J. Gaule, *Deutsch. med. Wochenschr.*, Nos. 19 and 24: 1896; W. S. Hall, *Arch. f. Anat. u. Physiol.*, p. 49: 1896; Hochhaus u. Quincke, *Arch. f. exper. Path. u. Pharm.*, vol. xxxvii. p. 159: 1896.

[4] Bidder u. Schmidt, "Die Verdauungssäfte u. d. Stoffwechsel," Mitau u. Leipzig, p. 411: 1852.

[5] C. Lehmann, Fr. Mueller, J. Munk, H. Senator u. N. Zuntz, Virchow's *Arch.*, vol. cxxxi. Suppl., pp. 18 and 67: 1893.

[6] Fritz Voit, *Zeitschr. f. Biolog.*, vol. xxix. p. 325: 1893.

with the same procedure as in Thiry's experiment (see p. 172), the only difference being that after the isolated piece of intestine had been cleansed, *both* ends were sewn up; the piece of intestine was then replaced, and the abdominal wound closed. The animals were fed upon meat for three weeks, at the end of which time they were killed, and the iron was estimated both in the contents of the isolated length of intestine and in the feces which had been formed in the remaining part of the intestines during the period of the experiment. Per unit area of mucous membrane, as much iron was found in the isolated coil as in the feces obtained from the remaining intestine.

If reduced iron were added to the meat diet, the proportion of iron in the contents of the isolated piece was not increased. From these experiments Voit concludes that the iron contained in normal diet is absorbed by the intestinal wall, and again excreted through the intestinal wall; and that, on the other hand, the inorganic preparations of iron administered artificially are not absorbed to any appreciable extent.

The objection to this last deduction is that the inorganic iron when absorbed may be eliminated only in certain sections of the intestinal tube, and that this particular isolated portion did not have that power. This question may therefore be regarded as still undecided.

But if we accept the conclusion that the inorganic forms of iron are not absorbed, it follows that our food must contain other combinations of organic iron,[1] which are assimilable and serve as the precursors of hemoglobin. I have sought to discover the nature of these compounds, using the yolk of egg as the basis for my experiments.[2] Yolk of egg does not contain any hemoglobin; but it must contain a precursor of this substance, since hemoglobin is found in the egg during incubation without the introduction of any material from without. I succeeded in isolating this precursor in a quantity sufficient for an exact research. If the yolk of hens' eggs be extracted with alcohol and ether, no iron passes out with the extract, but remains in the residue, which forms one-third of the dried substance of the yolk and consists of proteids and nucleins. The large amount of iron in this residue does not occur in the form of a salt, as may be proved by the fact that it cannot be extracted with alcohol containing hydrochloric acid; whereas all salts of iron, whether in combination with inorganic or organic acids—and amongst

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[1] Kletzinsky, *loc. cit.*, ascribes this theory in the first place to Hannon, whose writings are not accessible to me. But the existence of organic compounds of iron in our food has in nowise been proved by either of these authors.

[2] G. Bunge, *Zeitschr. f. physiol. Chem.*, vol. ix. p. 49: 1884.

these we must reckon proteids—at once yield their iron to the acid alcohol. The remainder of the yolk of egg which is insoluble in ether, dissolves readily in very dilute (1 per M.) hydrochloric acid. If to this solution tannic or salicylic acid be added, a white precipitate is thrown down ; but if even the slightest trace of ferric chlorid be shaken up with this solution, and it be now treated with tannic or salicylic acid, it turns either of a blue or red color respectively.

Iron occurs in yolk of egg as a nucleo-albumin. In artificial gastric digestion of yolk of egg, the proteids are converted into peptones, and the iron remains in the indigestible insoluble residue, the nuclein.[1] As in the case of the original compound, the iron in this nuclein cannot be extracted by hydrochloric acid alcohol. The iron is slowly split off by a watery solution of hydrochloric acid, and more quickly according to the concentration of the acid.

The nuclein-iron compound is soluble in ammonia. If to the ammoniacal solution some potassium ferrocyanid and excess of hydrochloric acid be added, a precipitate is produced, which is at first white, and gradually becomes blue, the change occurring more rapidly as the concentration of the hydrochloric acid is increased. If, instead of the ferrocyanid, potassium ferricyanid and hydrochloric acid be added to the ammoniacal solution, the precipitate remains white. The iron is therefore split off from the organic compound as ferric, and not as ferrous, oxid.

If to the ammoniacal solution of the iron-nuclein compound a drop of ammonium sulphid be added, no change of color is at first observed : after a little time, however, the solution takes a slightly greenish tinge, which increases in intensity until finally the next day it becomes black and opaque. The change in color proceeds with greater rapidity according to the amount of ammonium sulphid added. Ammoniacal solutions of artificial albuminates of iron change color almost instantaneously when treated with ammonium sulphid.

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[1] A nuclein was first prepared by Miescher from the yolk of egg. His method of preparation was however different from mine, and I imagine that the iron had been mostly split off from the compound by the action of the hydrochloric acid in the gastric juice. Otherwise the large amount of iron could not have escaped Miescher's notice. In my preparation the pepsin ferment acted only a very short time on the solution of the nucleo-albuminates in very dilute hydrochloric acid. In Miescher's preparation the yolk of egg, after extraction with ether and alcohol, was allowed to digest for 18 to 24 hours in gastric juice, containing 3 to 4 per mille HCl (10 ccm. of fuming HCl to 1 liter of water), at a temperature of 40° C. In my method of preparation the hydrochloric acid amounted only to a little over 1 per mille, and the solution was kept at body temperature only until the iron-nuclein compound began to separate out of the solution as a cloudy precipitate. (*Vide* Miescher, in Hoppe-Seyler's *Med. chem. Unters.*, pp. 454 and 504: 1871.)

Iron therefore is more closely combined in the nuclein of yolk of egg than in the iron albuminates, but far more loosely than in hematin, in which it cannot be detected by means of the ordinary reagents.

The elementary analysis of the iron-nuclein compound gave the following composition :

C	42.11	P	5.19
H	6.08	Fe	0.29
N	14.73	O	31.05
S	0.55		

This compound is undoubtedly the precursor of hemoglobin, since there are no other iron compounds present in any quantity in yolk of egg. I have therefore suggested that this substance should be termed hematogen (blood-forming).[1] If we imagine the phosphorus to have been split off from the hematogen as phosphoric acid, we get a molecule containing the same amount of iron as hemoglobin. The hemoglobin of hen's blood possesses 0.34 per cent. Fe.[2]

Following the same method by which I prepared hematogen from hens' eggs, an exactly similar compound was obtained from carps' eggs in Kossel's[3] laboratory. The elementary analysis of this compound gave the following figures :

	Preparation I.	Preparation II.
C	48.0	47.8
H	7.2	7.2
N	14.7	12.7
S	0.30	—
P	2.4	2.9
Fe	—	0.25

That hematogen may be absorbed and assimilated is shown by the experiments carried out by C. A. Socin[4] in my laboratory. Mice fed on an artificial diet, which contained no compound of iron except hematogen, lived for a hundred days, and gained in weight.

In our most important articles of vegetable diet the iron is also united loosely with organic substances as in hematogen.

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[1] The name hemoglobinogen would be more suitable but too lengthy. The name hematogen has been objected to on the score that it already occurs in medical nomenclature as an adjective: "hematogenic icterus." But as recent research has shown that there is no such thing as hematogenic icterus, we shall soon be able to do without the term altogether.

[2] A. Jaquet (Bunge's laboratory), *Zeitschr. f. physiol. Chem.*, vol. xiv. p. 289: 1889.

[3] G. Walter, *Zeitschr. f. physiol. Chem.*, vol. xv. p. 489: 1891.

[4] C. A. Socin (Bunge's laboratory), *Zeitschr. f. physiol. Chem.*, vol. xv. p. 93: 1891.

But the attempt to isolate these compounds is attended with much greater difficulty, since several different kinds are here met with.

I found it particularly hard to prepare iron-compounds from milk, because not only does the iron occur in union with various substances, but it is also present in very small quantities. A glance at the following table[1] will show that there is less iron in milk than in almost any other article of food:

One Hundred Grms. Dried Substance Contain the Following Amounts of Iron in Milligrammes.

Blood serum	0
White of hen's egg	Trace
Rice	1.0–2.0
Pearl barley	1.4–1.5
Wheat flour (sifted)	1.6
Cow's milk	2.3
Human milk	2.3–3.1
Dog's milk	3.2
Figs	3.7
Raspberries	3.9
Hazel nuts (kernel only)	4.3
Barley	4.5
Cabbage (inside yellow leaves)	4.5
Rye	4.9
Almonds (peeled)	4.9
Wheat	5.5
Bilberries	5.7
Potatoes	6.4
Peas	6.2–6.6
Cherries (black, without stones)	7.2
Beans (white)	8.3
Carrots	8.6
Wheat-bran	8.8
Strawberries	8.6–9.3
Linseed	9.5
Almonds (brown skins)	9.5
Cherries (red, without stones)	10
Hazel nuts (brown skins)	13
Apples	13
Dandelion leaves	14
Cabbage (outer green leaves)	17
Beef	17
Asparagus	20
Yolk of egg	10–24
Spinach	33–39
Pig's blood	226
Hematogen	290
Hemoglobin	340

This fact caused me surprise, as *à priori* I had anticipated the contrary, viz., that milk, being the exclusive food of the growing organism which is always increasing its blood-supply, would contain more iron than the food of full-grown animals which merely have to maintain their previous store of iron. The small amount of iron in the milk is the more remarkable since all other inorganic food-stuffs are contained in milk in just the proportion in which they are needed for the growth of the sucking animal.

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[1] The original sources, from which all the analyses in this table are taken, are given by G. Bunge, *Zeitschr. f. physiol. Chem.*, vol. xvi. p. 174: 1891; and by E. Häusermann (Bunge's laboratory), *Zeitschr. f. physiol. Chem.*, vol. xxiii. p. 586: 1897.

ONE HUNDRED PARTS BY WEIGHT OF ASH CONTAIN:

In	New-born Puppy.	Dog's Milk.
K_2O	11.42	14.98
Na_2O	10.64	8.80
CaO	29.52	27.24
MgO	1.82	1.54
Fe_2O_3	0.72	0.12
P_2O_5	39.42	34.22
Cl	8.35	16.90

With the exception of the iron, the relative proportion of the remaining constituents in the ash is almost identical. The object of this uniformity is evidently to ensure the greatest possible economy. The maternal organism gives nothing which cannot be utilized by the offspring. An excess of any constituent would be wasted. This marvellous adaptation of means to an end appears however to be rendered futile by the small amount of iron in the ash of milk: it is six times less than that in the ash of the sucking animal. According to this, the maternal organism would seem to part with six times too much of the remaining constituents to its offspring. Apparently only one-sixth can be employed to build up the organs, and the remaining five-sixths are thrown away!

The explanation of this contradiction is that the young animal contains at birth a large store of iron for the growth of its tissues. In a series of estimations of iron in the total organism of young dogs, cats, and rabbits, I have shown that the amount of iron is the highest at birth, and that it gradually diminishes afterwards.[1] At least five times more iron is found in the liver of new-born than in that of full-grown animals. In the same way the other tissues must possess their store of iron which can be drawn upon to meet the rapid development of the blood.

The advantage of this arrangement seems to be as follows: The assimilation of organic compounds of iron is obviously attended with great difficulty, hence the maternal organism uses up its acquired store with the greatest economy. The amount which must be conveyed to the infant organism can reach it in two ways: through the placenta and through the mammary glands. The former way is preferred as the more secure. If the main proportion of the organic compounds of iron was conveyed by the mammary gland, it might become a prey to bacteria in the alimentary canal and before absorption had begun. But if it reaches the fetus through the placenta, its safety is assured.

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[1] G. Bunge, *Zeitschr. f. physiol. Chem.*, vol. xvi. p. 177 : 1891, and vol. xvii. p. 63: 1892.

In the following table[1] I give the figures for the amount of iron in young rabbits and guinea-pigs.

RABBITS. (Age of the animals.)	Mg. Fe to 100 grms. body-weight.
Embryos arranged according to increasing body-weight.	6.4 8.5 9.0
1 hour after birth	18.2
1 day " "	13.9
4 days " "	9.9
5 " " "	7.8
6 " " "	8.5
7 " " "	6.0
11 " " "	4.3
13 " " "	4.5
17 " " "	4.3
22 " " "	4.3
24 " " "	3.2
27 " " "	3.4
41 " " "	4.5
45 " " "	4.2
46 " " "	4.1
74 " " "	4.6

GUINEA-PIGS. (Age of the animals.)	Mg. Fe to 100 grms. body-weight.
Embryos	4.6 4.4 5.6 5.3 5.0
6 hours after birth	6.0
1½ days " "	5.4
3 " " "	5.7
5 " " "	5.7
9 " " "	4.4
15 " " "	4.4
22 " " "	4.4
25 " " "	4.5
53 " " "	5.2

I have ascertained from repeated and continued investigation of the gastric contents that young rabbits are nourished during the first fortnight exclusively on the mother's milk. About the middle of the third week they begin to take vegetable food as well as the milk, and in the fourth week the stomach contains principally vegetable matter. As the above figures show, the fourth week is the time when the store of iron has become used up and the amount of iron in proportion to the body-weight has reached its minimum. With the commencement of a vegetable dietary rich in iron, the amount of this substance in the body again begins to rise.

The case of guinea-pigs is very different. These animals begin by eating vegetable food from the first day and select by preference the leaves which are very rich in iron, and during the subsequent days milk plays but a subordinate part compared to this form of food. And correspondingly we find that (as may be seen from the above figures) guinea-pigs have at birth a very small store of iron in their organs. Thus in these two nearly related animal species, Nature herself has made an *experimentum crucis*, which confirms my conception concerning the significance of the store of iron provided for new-born animals.

Very little iron is assimilated from the milk during the

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[1] G. Bunge, *idem*.

suckling period. In the young rabbit the absolute amount of iron remains nearly constant, whereas the body increases in weight sixfold by the end of the fourth week. The relative proportion of iron therefore falls to one-sixth, as reference to the above table will show. The animals at this time appear to be already anemic. But they now begin to take food containing abundance of iron, when the amount of this substance at first rises. Subsequently the absolute quantity of assimilated iron grows in proportion to the body-weight, and the relative amount remains nearly constant. If the attempt were made to feed the young animals exclusively with milk after the period of suckling had elapsed, they would certainly become anemic.

This condition of anemia has been utilized by me to decide the question as to the assimilability of inorganic iron. At the end of lactation, the young animals were fed entirely on milk, or on milk and rice. Rice, as we may see from the table, is even poorer in iron than milk. One half of the animals employed in this experiment received in addition to this food, a small quantity of ferric chlorid daily. After this diet had been given from one to three months, and the animals had doubled their weight, they were killed and the amount of hemoglobin in the total body was estimated, as well as, in the case of small animals, the amount of iron.

In this manner E. Häusermann carried out experiments in my laboratory on 24 rats, 17 rabbits, 14 dogs, and 3 cats. The rats all became highly anemic; for at the end of the experiment the percentage of hemoglobin was diminished to about half that of animals from the same litter which had received their normal food—meat, flies, yolk of egg, fruit, vegetables. The rats, which had taken ferric chlorid in addition to the milk and rice, contained no more hemoglobin than those which had received milk and rice only. Moreover the amount of iron was in each case the same. In one experiment alone, in which the addition of ferric chlorid was continued for three months, was the iron found to be double as much in the animals which received it as in those which had only milk and rice. But here again the proportion of hemoglobin remained the same in both instances. We thus see that some iron is absorbed if small doses of iron are persisted in for a long time, as well as if large amounts be suddenly administered. But this inorganic iron, when absorbed, is not utilized in the formation of hemoglobin to any appreciable extent, but remains unused in the tissues. Whether inorganic iron was absorbed in the experiments, which lasted only from one to two months, cannot be decided: it is possible that same of it was absorbed and was again eliminated in the same degree. Certainly no storing up nor increase of iron could be detected in the whole organism.

The experiments on rabbits gave less decisive results: the average proportion of hemoglobin in the animals that received iron was somewhat higher than that in the animals which were fed on milk and rice only. But if the great individual differences between various animals be taken into consideration, I do not think we must ascribe too much importance to this slight divergence. At any rate the amount of hemoglobin in the control animal, which received its normal diet—fresh green cabbage, bran, etc.—was nearly twice as high as in the animal which received the iron.

The experiments on dogs were not attended with decisive results. Dogs are not suitable animals for these experiments owing to their individual differences. Moreover the growth of these animals after the period of lactation is at a much slower rate, and their appetite so enormous that they might be readily able to assimilate sufficient hemoglobin even from a material so poor in iron as milk, while their appetite remained normal. Häusermann found the largest proportion of hemoglobin in a dog which had been fed exclusively with milk. The animals which received ferric chlorid in addition to a milk diet certainly contained no more hemoglobin than animals from the same litter which were fed on meat and bones. Cloetta[1] carried out some experiments on the same principle as ours, and came to the conclusion that iron was assimilated in its inorganic form. We are not at present in a position to corroborate this statement.

Häusermann further conducted a research on the question as to whether the hemoglobin of the food was assimilable. It appeared that young rats, which were given dried, powdered hemoglobin in addition to milk and rice, formed twice as much hemglobin as the animals from the same litter, which received milk and rice alone. The hemoglobin of the food therefore appears to be absorbed and assimilated. This experiment with hemoglobin was however performed on only two animals, and I intend therefore to repeat it.

In order to obviate misapprehension,[2] I may be allowed

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[1] M. Cloetta, *Arch. f. exper. Path. u. Pharm.*, vol. xxviii. p. 161: 1897.

[2] My previous publications on the iron question have been continually misrepresented by the medical press. In particular the statements which were made by me at the Clinical Congress at Münich in the spring of 1895 have been reported in quite a contrary sense. At the Congress I gave an account of the present state of the question from an objective standpoint, reserving my judgment, speaking sceptically and affirming nothing. Comp. *Verhandl. des Congresses f. inn. Med.*, Cong. xiii., Wiesbaden, Bergmann, pp. 133 and 191:

to shortly recapitulate the results of the investigations on the absorption and assimilation of inorganic iron :

1. So far it has not been proven that any part of the inorganic preparations of iron given in the small quantity (0.1–0.2 grm. Fe per diem) which is necessary in order to avoid digestive disturbances, is absorbed either in man or in the smaller animals, to which correspondingly less iron can be administered. We must however concede the possibility that small amounts may be absorbed.

2. If large quantities of iron be given, or if the administration of small doses be continued over a long period, part of the iron passes the intestinal wall. But it cannot be ascertained whether this iron is assimilated, although such a possibility cannot be denied.

3. Even if the assimilation of inorganic preparations of iron be granted, it is indisputable that the iron which exists in normal food in the form of organic compounds is far more readily and more completely absorbed.

Should further research show that inorganic iron is utilized in the production of hemoglobin, the fact would be of the greatest theoretical interest. It would furnish fresh proof that syntheses occur as complex in the animal as in the vegetable cell. Hitherto scientific men, steeped in Liebig's doctrine, have ascribed too little power to the animal cell. But even if the assimilation of inorganic iron was a proved fact, it would have no importance in medical practice since, as our experiments show, the iron required for the formation of hemoglobin is much more readily and plentifully assimilated from the organic iron-compounds of our normal dietary. Hence there is in no case any reason to prescribe preparations of iron for the production of hemoglobin in people who can take their natural food with a good appetite.

It is quite another question as to whether anemic patients should be given preparations of iron, not indeed as material for conversion into hemoglobin, but in order to influence the formation of blood in some indirect way. That these preparations may have such an effect cannot be denied, although there is so far no adequate proof on the matter. It is not sufficient evidence to say that the experience has been made; we must know how it has been done. Where are the statistics? Where are the control experiments?[1]

1895. I request that for the future I may be attacked only for what I have said, and not for what I have never said.

[1] Compare my critique of the therapeutics of iron in the *Verhandl. des Congresses f. inn. Med.*, Congr. xiii., Wiesbaden, Bergmann, pp. 143–147 and 191 : 1895.

If thus all previous experimentation teaches us decisively that iron is most surely and abundantly assimilated from our natural food, it follows that it is highly desirable for us to know the proportion of iron contained in the various articles of our diet. This knowledge will be of the greatest value both as a weapon and as a prophylactic against poorness of blood. Let us therefore again glance at the table on p. 376. It is a very surprising fact that, next to milk, the cereals, which are the most important articles of vegetable food, contain the least iron, that is to say, in the form in which they are generally consumed, when deprived of their husks, the so-called bran. Rice, as it comes into the market, is already deprived of its husk; it does not correspond to barley or wheat corn but to pearl barley or wheat flour. In sifting the flour, the husks, the so-called bran, are separated from the flour. From the table we see that the cereals, when freed from their husks, contain only half as much iron as milk. The iron of the cereals exists in the husks. Whole wheat-meal therefore contains five times as much iron as the ordinary wheat-flour.

This shows how irrationally anemic people are fed. We may take as an instance the poor bloodless seamstresses, who eat white bread and drink tea! With the aid of all our chemical knowledge we could not give to animals which we wished to make anemic any food with less iron it!

It would be very interesting to ascertain experimentally whether the iron compounds in the bran are assimilable. If this were so, whole meal bread would be preferable to white bread. I am now engaged on experiments with the object of deciding this question.

At the Münich Medical Congress Professor Heubner[1] stated that "15 kilograms of meat,[2] so far as I am aware, cost about thirty shillings, and that 300 Blaud's pills cost three shillings. I fear that a large number of people will continue to take the pills." I would, however, point out that there are many cheap articles of food which contain sufficient iron, such as potatoes, carrots, cabbage. But it is still an open question whether in the equally cheap leguminosæ, as in the cereals, the iron is not principally confined to the husks, and whether the iron in the husks is assimilable.

The danger of taking food which is too poor in iron is also present in children, who are nourished principally with milk for a long time after lactation has ceased. The normal duration

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[1] Heubner, *loc. cit.*, p. 174.

[2] I had estimated (*loc. cit.*, p. 144) that 15 kilos. meat contained 0.6 grm. Fe, or sufficient to produce one-third of the total hemoglobin in a man.

of suckling in human beings is unknown to us. The instincts of neither mother nor child give us any clue. Even the habits of aboriginal races furnish us with no data. Instinct is dying out, never to return; but it is the noble duty of science to replace unerring instinct by conscious knowledge. If we could determine the time at which the store of iron possessed by the infant at birth becomes used up in the organs, the problem would be solved. This solution would be practicable if estimations were made on the bodies of healthy children which had suddenly met with an accidental death. In the light of our present knowledge however, it seems probable that children are often rendered anemic by the milk diet being too prolonged or too exclusively employed; and I am pleased to hear that this observation of mine is confirmed by children's physicians of experience. For instance, Professor Heubner stated at the Münich Congress:[1] "For many years a number of children's physicians have recommended that a purely milk diet should not be continued too long towards the end of the suckling period. For about ten years I have myself adopted and have also taught the principle of giving other food as a supplement to milk after the infant has reached the age of 9 or 10 months, and this not only in cases of anemia, but also in other cachectic conditions of rickety children, although I am not able to adduce any reason for this treatment. I may add that I was very pleased to read the first work published by Professor Bunge on this subject, and have followed his experiments with the greatest interest. Since then I have found it highly beneficial to give even vegetables to young children. In my practice I have met with the greatest astonishment on the part of parents who consulted me, when I told them to give the child (which perhaps had eight teeth) a small spoonful of spinach or cabbage or something of the kind every day. This advice was however the result of a long and favorable experience. The advantage of this treatment must have recently become known in Berlin. A short time ago I was somewhat reproachfully asked by the father of an infant eight months old, which had not cut any teeth, why I did not order the child spinach and apple sauce. I am quite sure that this gentleman had no idea of Professor Bunge's investigations."

Dr. Freund wrote to me on April 19, directly after my communication at the Münich Congress: "I have long since observed and frequently state that an exclusive or even preponderating milk diet for children when they are weaned is not only insufficient, but also harmful, in that the children become

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[1] Heubner, *loc. cit.*, p. 174.

pale and weak, and suffer from poorness of blood. The children of the lower classes, especially in the country, with their rosy cheeks, might well be objects of envy to many mothers among the upper ten thousand, and I would point out that these children partake of the same food as their parents towards the end of their first year of life."

Professor Monti[1] of Vienna says in the article he has just published on weaning and nutrition: "If children be nursed up to the twelfth and fifteenth month, they do not grow as they should, even when the milk is sufficient in quantity. They become anemic, their muscles become flabby, and their development is delayed, so that, instead of attempting to walk at the end of the first year, they do not begin to do so until they are about eighteen or nineteen months old." "There are certainly a few races where it is customary to feed children at the breast after they have attained their first year. We have comparatively often had the opportunity of seeing some of these children, which are usually of Slavonic parentage, and in all cases the state of nutrition was a bad one. Other food than the mother's milk is imperatively indicated." "The custom of over-prolonged nursing exists in France, in a few parts of Italy, and, according to hearsay, in Japan. All authorities are agreed however that the continuation of the suckling beyond the proper time always induces disturbances in the child's nutrition, and that many cases of rickets must be ascribed to this practice."

The other day I came across a very interesting and doubtless unusual case, where an exclusive milk diet had been continued into adult life. A youth of eighteen, from the technical schools at Aarau, has lived on nothing but milk from the time of his birth. He states that he has occasionally tried a piece of bread or a pear, but that it had not agreed with him. He has an invincible dislike to all animal and vegetable food. His face is pale, as well as the mucous membrane of the tongue and of the conjunctivæ. He suffers from cold feet and hands, is easily tired in walking, and has palpitation of the heart when he goes upstairs. E. Häusermann found that, although his blood contained five million blood-corpuscles in the cmm., it had only 8.6 per cent. hemoglobin, whereas a normal person has 12–16 per cent. These are therefore conditions similar to those occurring in cases of chlorosis, viz., about the usual number of blood-corpuscles, with a diminished amount of hemoglobin.[2]

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[1] Alois Monti, "Ueb. d. Entwöhnung, Ernährung," &c., Wien. u. Leipzig, Urban u. Schwarzenberg, p. 104: 1897.

[2] Häusermann gives a detailed description of this case, *loc. cit.*, p. 585.

In order to obviate misunderstanding, I would, in conclusion, lay stress upon the fact that I do not maintain that all forms of anemia, and especially chlorosis, may be cured by a diet rich in iron. The etiology and the nature of chlorosis are entirely obscure, and any treatment with iron, even if it be only the iron in the food, is at the best but dealing with the symptoms. But in anemia, the first thing to do is to cease taking food which would make even a healthy person bloodless, and afterwards to think of medicines.

As regards treatment with drugs, I do not deny the use of medical experience on the old system. Any unprejudiced person of good memory may store up abundant statistical material, together with the needful control experiments, without writing down his observations and communicating them to his colleagues. As a matter of fact many thousands of experiences in other practical departments, which are likewise concerned with complex manifestations of life, such as farming, horticulture, cattle-breeding, hunting, fishing, are collected in this manner, and subsequently confirmed by science. But both in science and in practice it is good to demand strict proofs, proofs which may not only convince individuals, but may be binding on all experts as well as on future generations.

I therefore venture to make the following proposition with regard to the investigation into the action of iron. In the first place, cases of anemia as like each other as possible should be sought out. Half of these should be selected by lot and be treated with some definite preparation of iron, while the other half should receive no iron, but in its stead some indifferent medicine, with the assurance that this latter was an unfailing remedy. The time should then be determined at which the amount of hemoglobin and the number of blood-corpuscles had risen by a certain percentage. Disturbing factors, such as the varying idiosyncrasies of the different cases, can only be eliminated by taking a sufficiently large number of cases for the experiment. In private practice we shall always have to deal with the difficulty of being able to ensure that the medicine prescribed is really taken. I myself have known of many cases where the doctor triumphantly ascribed the credit of the chlorotic patient's red cheeks to the influence of the Blaud pills, whereas, as a matter of fact, not a single pill had been taken.

LECTURE XXVI

DIABETES MELLITUS

In our remarks on metabolism in the liver, and on the source of muscular energy, we became acquainted with the destiny of carbohydrates in the body, and with the way in which they are utilized under normal conditions. We are now therefore in a position to consider the intricate investigations concerning the destiny of carbohydrates under pathological conditions, and especially the researches into the causes and nature of diabetes mellitus. This is a subject with touches on all branches of physiological chemistry, and about which a complete library of books[1] has been written, the references to which would alone form a good-sized volume.

These remarks will be confined to the chronic form of diabetes. Transient glycosuria[2] occurs as a consequence, and sometimes as an unimportant symptom in a great variety of maladies, such as zymotic diseases, digestive disturbances, neuralgia, cerebral concussion and hemorrhage, cerebro-spinal meningitis, epilepsy, psychical excitement, poisoning by various substances,[3] &c. No satisfactory explanation to account for the appearance of glycosuria in all these cases has yet been given, and it would lead us too far to discuss all the maladies of which glycosuria forms a symptom.

But even if we confined ourselves to that chronic disorder which is strictly termed diabetes, a complete account of the disease and its numerous and varying symptoms would be

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[1] An account of the most important works on diabetes mellitus is given by Cl. Bernard, "Leçons sur le diabète": Paris, 1877; Ed. Külz, "Beiträge zur Pathologie und Therapie des Diabetes mellitus": Marburg, 1874 and 1875; Frerichs, "Ueber d. Diabetes": Berlin, 1884. Frerichs has watched no less than four hundred cases of diabetes, and has recorded the results of his wide experience in a clear, comprehensive, and critical work, especially remarkable for its objectivity. We strongly recommend this book to the student. Compare also F. W. Pavy, "On the Nature and Treatment of Diabetes," 2d edit., London; and J. Seegen, "Der Diabetes mellitus," Aufl. ii.: Berlin, 1875; and Arnoldo Cantani, "Der Diabetes mellitus." Deutsch von S. Hahn: Berlin, 1880.

[2] Frerichs (*loc. cit.*, pp. 25–61) gives a comprehensive account of all forms of transient glycosuria.

[3] Of these substances, phloridzin must be particularly mentioned; its glycosuric action on animals containing no glycogen has been already noticed (p. 346).

beyond the scope of the present lecture. It is merely our intention to collect the chief results of the experimental investigations carried out for the purpose of determining the causes and nature of this disease.

Up to the present, pathological anatomy has led to no conclusion. Post-mortem examination of the bodies of diabetics proves that there is not a single organ which does not occasionally show anatomical changes; on the other hand, there is not a single organ that does not frequently appear normal. It is likewise impossible, in all cases, to decide whether these anatomical changes are the cause or the consequence of the chemical changes.[1]

We will therefore restrict ourselves to the consideration of those data which bear upon physiological chemistry. The most obvious symptom, the occurrence of sugar in the urine, has always formed the basis of these observations.

As already stated, normal urine contains no sugar, or at most a trace. In diabetes, often a very considerable amount is found, varying from a few grammes to one kilogramme in twenty-four hours' urine. This sugar is invariably dextrorotatory grape-sugar.[2] With many patients who have the disease in a mild form, the sugar disappears from the urine if carbohydrates are excluded from the diet; with others who are more seriously affected, the excretion of sugar continues, even though an exclusive meat diet be adopted. In what way can we account for the appearance of this large amount of sugar in the urine?

Only two suppositions are open to us. Either the kidneys have lost their power of preventing the sugar, normally present in the blood, from passing into the urine; or else the kidneys have retained their usual function, but the amount of sugar in the blood has abnormally increased.

The latter supposition must be regarded as the correct one; for the former would imply that there is less than the normal amount of sugar in the blood of diabetic patients, whereas the quantity found is, as a matter of fact, always above the normal.[3] The blood of man and of the dog normally

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[1] Frerichs (*loc. cit.*, pp. 144–183) gives a comprehensive and instructive tabulated account of the results of fifty-five autopsies.

[2] J. Seegen states that he has found levorotatory sugar in the urine of a person suffering from 'diabetes intermittens' (*Centralbl. f. d. med. Wissensch.*), No. 43: 1884. Compare E. Külz, *Zeitschr. f. Biolog.*, vol. xxvii, p. 228: 1890, where a critical summary will be found of all the statements relating to the occurrence of levorotatory sugar in urine.

[3] A diminution of the sugar in the blood is found in phloridzin diabetes. This is therefore a different condition to the 'natural' diabetes, and cannot be directly applied to the explanation of the latter condition. In phloridzin diabetes it is

contains from 0.05 to 0.15 per cent. of sugar; the blood of diabetic patients from 0.22 to 0.44 per cent.[1] If the proportion of sugar in a dog's blood be artificially increased to more than 0.3 per cent. by the injection of a solution of this substance, sugar passes through the normal kidneys into the urine. No affection of the kidneys has ever been discovered in the first stages of diabetes.

It is therefore certain that an abnormal increase of sugar in the blood is the cause of the appearance of sugar in the urine.

We now come to the question as to the cause of the increase of sugar in the blood, and again we have to choose between two explanations. There must be either a larger quantity of sugar formed, or a smaller amount of sugar decomposed.

The first explanation cannot be accepted, for from what could the large proportion of sugar be formed? Not from the other carbohydrates, as this would be a normal process; not from the fats, as diabetic patients can digest and assimilate them in large quantities.[2] As to the proteids, assuming that a diabetic patient consumed 300 grms.[3] in a day (which it would be difficult to do), even this amount of proteid would not form more than about 200 grms. of sugar; for a large proportion of the carbon must be given off with the nitrogen. But even if 200 grms. of sugar reached the blood in the course of each day, it would not cause diabetes, so long as the decomposition of sugar remained normal. A man, on a diet of potatoes, will form from 600 to 1000 grms. of sugar per diem from the starch in his food, without any sugar passing into the urine.

We must therefore accept the other explanation, that the increase of sugar in the blood of diabetic patients is due to a diminished sugar destruction.

The power of decomposing sugar is never entirely arrested;

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probably the kidneys which are primarily at fault. Compare Minkowski, *Berlin. klin. Wochenschr.*, No. 5 : 1892; and "Untersuch. üb. d. Diabetes mellitus," p. 64 : Leipzig, 1893.

[1] Carl Bock und Frdr. Albin Hofmann, "Experimentelle Studien über Diabetes," p. 61 : Berlin, 1874; Frerichs, *loc. cit.*, p. 269.

[2] Pettenkofer and Voit, *Zeitschr. f. Biolog.*, vol. iii. pp. 406, 408, 416, 428, 436 : 1876. L. Block (*Deutsch. Arch. f. klin. Med.*, vol. xxv. p. 470 : 1880) found that only 9 grms. out of from 120 to 150 grms. of fat reappeared in the feces of diabetic patients.

[3] With a diabetic patient, the urea excreted in twenty-four hours seldom amounts to more than 100 grms., which corresponds to 300 grms. of proteid. Pettenkofer and Voit (*loc. cit.*, p. 424) found from 46 to 86 grms. of urea in a severe case of diabetes, the patient being allowed to eat whatever he liked.

it is only more or less impaired. Külz[1] has shown that, even in severe cases of diabetes, there is a smaller amount of sugar in the urine than would correspond to the carbohydrates of the food.

We will now proceed to inquire how the power of splitting up sugar is impaired — a question which again appears to be capable of but two answers. We are only acquainted with two processes by which the food-stuffs are destroyed in our tissues: decomposition and oxidation. One of these two processes must be diminished.

No decline in the process of oxidation in diabetes has so far been proved from observations and experiments. The ultimate products of proteid combustion are normal, and the fat appears to be completely oxidized to carbonic acid and water. Salts of vegetable acids and lactates reappear in the urine as carbonates.[2] Benzol is oxidized to phenol.[3] Certain carbohydrates even (such as levulose, inulin and inosit), and mannite, which is so closely related to the carbohydrates, are decomposed.[4] How is it that grape-sugar alone remains unoxidized?

That oxidation is not impeded is further proved by the circumstance that no increase of sugar in the blood, or passage of sugar into the urine,[5] has ever been observed either in diseases connected with disturbances of external and internal respiration, or in artificial respiratory disturbances.[6]

We must therefore conclude that the grape-sugar cannot be oxidized because its decomposition is impeded; decomposition must precede oxidation; if the former be impaired, the latter cannot take place, although neither external nor internal respiration is disturbed.

O. Schultzen[7] endeavored to support this view by com-

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[1] Külz, "Beitr. z. Path. u. Therap. d. Diabetes mellitus," pp. 110–119: Marburg, 1874.

[2] O. Schultzen, *Berliner klin. Wochenschr.*, No. 35: 1872; Nencki and Sieber, *Zeitschr. f. prakt. Chem.*, vol. xxvi. p. 34: 1882.

[3] Nencki and Sieber, *loc. cit.*, p. 36.

[4] E. Külz, "Beitr. z. Path. u. Therap. d. Diabetes mellitus," pp. 127–175: Marburg, 1874. The experiment with mannite does not seem to be convincing, because borborygmi, flatulence, and diarrhea occurred after taking it. It is possible that the mannite introduced was mostly decomposed by fermentative organisms in the alimentary canal. A small amount was found unaltered in the urine. With respect to inosit, *vide* also E. Külz, *Sitzungsber. d. Ges. z. Beförderung d. ges. Naturw. zu Marburg*, No. 4: 1876.

[5] Von Mering, *Arch. f. Physiol.*, p. 381: 1877.

[6] Senator, Virchow's *Arch.*, vol. xlii. p. 1: 1868.

[7] O. Schultzen, *loc. cit.* The view that sugar could only be oxidized subsequently to decomposition was first suggested by Scheremetjewski in a research published from C. Ludwig's laboratory (*Arb. aus d. physiol. Anstalt zu Leipzig*, p. 145: Jahrg. 1868; Leipzig, 1869). Compare also Nencki and Sieber, *loc. cit.*, p. 39.

paring observations on diabetics with those on persons suffering from phosphorus-poisoning. As we have already seen (p. 363), oxidation is diminished in cases of phosphorus-poisoning. Instead of sugar, lactic acid occurs in the urine; and this Schultzen regarded as a normal product of the decomposition of grape-sugar. He therefore said that, after phosphorus-poisoning, the power of oxidation was lost, but not that of decomposition, while the reverse was the case in diabetes. Hence, after phosphorus-poisoning, the normal product of decomposition appears in the urine, while in diabetics, in spite of undisturbed oxidation, the unaltered grape-sugar appears in the urine.

The following experiment of Pettenkofer and Voit[1] may be interpreted in the same way. By means of their respiratory apparatus, they showed that a diabetic took in less oxygen and excreted less carbonic acid than a healthy person.

It was not that less sugar was broken up because the income of oxygen was reduced, but that less oxygen was used up because the formation of oxidizable products of decomposition was diminished.

This theory is very inviting, but objections may be raised to it. The fact, already mentioned in our remarks concerning internal respiration (p. 259), that certain substances, after introduction into the body, appear in the urine conjugated with glycuronic acid, is opposed to the view that decomposition must precede oxidation. Glycuronic acid is undoubtedly a product of oxidation, but not of decomposition; all six atoms of carbon are still united, and yet oxidation has begun. Conjugation alone prevents its completion; and as soon as the compound is split up, nothing can stop its further progress.

Nencki and Sieber say, "We do not doubt that, if the diabetic could break up sugar to form lactic acid, he would afterwards be able completely to oxidize the sugar."[2] But lactic acid is evidently not the normal product of decomposition of sugar in the body. The sarcolactic acid, which is invariably present in the organs, probably arises from proteid (p. 312). As nothing is yet known concerning the course and sequence of the decomposition and oxidation of sugar in the organism under normal conditions, we are scarcely in a position to inquire into the abnormal chemical processes occurring in diabetes.

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[1] Pettenkofer and Voit, *Zeitschr. f. Biolog.*, vol. iii. pp. 428, 429, 431, and 432: 1867.

[2] Nencki and Sieber, *Journ. f. prakt. Chem.*, vol. xxvi. p. 37: 1882.

Attention must be particularly called to the occurrence in the diabetic urine of substances which are evidently products of incomplete oxidation: oxybutyric acid, aceto-acetic acid, and aceton.[1] They probably arise from the proteids, for their amount is independent of any addition of carbohydrates to the diet, but increases with increased proteid metabolism.[2] They do not occur in all cases of diabetes, but generally in the more severe forms of the disease, in which the destructive metabolism of proteid is augmented.

The oxybutyric acid in diabetic urine is the levorotatory β-oxybutyric acid ($CH_3-CH(OH)-CH_2-COOH$). The aceto-acetic acid ($CH_3-CO-CH_2-COOH$), which can be artificially produced by oxidation from β-oxybutyric acid, breaks up readily into aceton and carbonic acid: $CH_3 - CO - CH_2 - COOH = CH_3 - CO - CH_3 + CO_2$. The aceto-acetic acid and the aceton in diabetic urine have probably originated in the same way in the organism.

In the last stage of diabetes, when coma sets in, the amount of oxybutyric acid increases, while that of aceton diminishes.[3] This fact also appears to argue in favor of an increasing decline in the power of oxidation.

It must however be noted that the occurrence of oxybutyric acid, aceto-acetic acid, and aceton is not confined to diabetes, but has been observed in many other maladies.[4] These anomalous products of metabolism may possibly be a direct consequence, not of diabetes itself, but of certain complications which frequently accompany the disease.

On the other hand, it must be remembered that wasting of the tissues and general cachexia, in short, increased destruction of the nitrogenous constituents of the body, invariably take place in all the diseases in which acetonuria has been observed, such as febrile infectious diseases, carcinoma, mental affections

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[1] Stadelmann, *Arch. f. exper. Path. u. Pharm.*, vol. xvii. p. 419: 1883; and *Zeitschr. f. Biolog.*, vol. xxi. p. 140: 1885; Minkowski, *Arch. f. exper. Path. u. Pharm.*, vol. xviii. pp. 35, 147: 1884; E. Külz, *Zeitschr. f. Biolog.*, vol. xx. p. 165: 1884; and vol. xxiii. p. 329: 1886; and *Arch. f. exper. Path. u. Pharm.*, vol. xviii. p. 291: 1884; Rud. von Jaksch, "Ueber Acetonurie u. Diaceturie": Berlin, 1885; H. Wolpe, *Arch. f. exper. Path. u. Pharm.*, vol. xxi. p. 138: 1886; Frerichs, *loc. cit.*, pp. 114–118.

[2] G. Rosenfeld, *Deutsch. med. Wochenschr.*, No. 40: 1855; Wolpe, *loc. cit.*, pp. 150–155. The older literature is here quoted. Also M. J. Rossbach, *Correspondenzblatt des allgem. ärztlichen Vereins für Thüringen*, No. 3: 1887; *Chem. Centralbl.* p. 1437: 1887.

[3] Wolpe, "Unters. ü. d. Oxybuttersäure des diabetischen Harnes," Dissert.: Königsberg, 1886; *Arch. f. exper. Path. u. Pharm.*, vol. xxi. p. 157: 1886.

[4] R. von Jaksch, "Ueber Acetonurie u. Diaceturie," pp. 54–91: Berlin, 1885; Külz, *Zeitschr. f. Biolog.*, vol. xxiii. p. 329: 1886; A. Baginsky, Du Bois' *Arch.*, p. 349: 1887.

accompanied by inanition, &c. The occurrence of aceto-acetic acid has likewise been noticed in the urine of healthy persons after prolonged fasting.[1] Increased decomposition of proteid now appears to be an accompaniment of diabetes also: at least, it was proved, by careful experiment in three severe cases, that the patient excreted more nitrogen than a healthy person on exactly the same diet. The first investigation of the kind was carried out by Gaehtgens[2] in his clinique at Dorpat, the second by Pettenkofer and Voit,[3] and the third by Frerichs.[4]

These experiments might be taken to mean that the increased decomposition of proteids in diabetes was a consequence of the inadequate breaking up of the sugar; that, because the chemical potential energy of the sugar was not completely utilized, the proteid must assist in furnishing the kinetic energy necessary for the performance of the functions of the body. This would be analogous to the behavior of normal muscle, which, as we have seen, has recourse to its store of proteid as soon as the supply of non-nitrogenous food runs short. But this is only a teleological, not a physico-chemical explanation, and gives no account of the causal connection. We must concede the possibility that the increased decomposition of proteid may be the first sign of disturbance in the metabolism of the organs, and may usher in the wasting of the tissues and all the other troubles. It may be also that the occurrence of oxybutyric acid, aceto-acetic acid, and aceton in diabetes is not due to the reduced supply of oxygen, any more than it is in the case of the other diseases mentioned. The tissues may receive their normal supply of oxygen, but the products of decomposition may have risen above the normal amount; and that part of them which reaches the blood in a state of incomplete oxidation, cannot be further oxidized there because, as we have already seen (p. 247), no processes of oxidation take place in the blood.

The power possessed by a diabetic of utilizing levorotatory sugar is a remarkable fact, which was observed by Külz.[5]

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[1] See the interesting notice in the report of the investigations carried out on the 'professional faster,' Cetti, in Berlin (*Berliner Wochenschrift*, vol. xxiv. p. 434: 1887).

[2] Carl Gaehtgens, "Ueber den Stoffwechsel eines Diabetikers, verglichen mit dem eines Gesunden," Dissert.: Dorpat, 1886.

[3] Pettenkofer and Voit, *Zeitschr. f. Biolog.*, vol. iii. pp. 400, 408, 412–414, 425. An account of the older literature will be found here, pp. 425–426.

[4] Frerichs, *loc. cit.*, p. 276, *et seq.*

[5] Külz, *loc. cit.*, pp. 130–167. Also Worm-Müller, Pflüger's *Arch.*, vol. xxxiv. p. 576: 1884; S. de Jong, "Overomzetting van milksuiker by diabetes mellitus," Dissert.: Amsterdam, 1886; and Franz Hofmeister, *Arch. f. exper. Path. u. Pharm.*, vol. xxv. p. 240: 1889.

He showed that after eating 100 grms. of levorotatory fruit-sugar, no sugar appeared in the urine of a patient who was but slightly affected with the disease, and that the amount of sugar, which consisted only of dextrorotatory grape-sugar, was not increased in the urine of a patient who had a severe form of diabetes.

Inulin behaves in the same manner as levulose. It is found in the roots of elecampane, chicory, and dandelion, and in the tubers of dahlias, where it plays the same part as the starch in the potato tubers. Inulin stands in the same relation to levulose as starch does to dextrose: on boiling with dilute acid, it is split up with hydration to form levulose, just as starch is changed into dextrose. Inulin evidently undergoes this decomposition in the organism as well; like levulose, it is consumed in the body of a diabetic.

It is well known that, on boiling with acids as well as by the action of ferments, cane-sugar is split up into equal quantities of levulose and dextrose. In conformity with this, Külz observed that, after the administration of cane-sugar in the aggravated form of diabetes, the increase in the excretion of dextrose was equal to half the amount of the cane-sugar eaten. These experiments of Külz on the fate of levorotatory sugar in diabetics have since been repeated many times.[1] The results are however contradictory, and it appears that different patients vary in their power of utilizing this sugar. In general, the statement that levorotatory sugar is entirely or in greater part assimilated has been confirmed. In many cases, however, a small quantity of dextrorotatory sugar appeared in the urine as a result of the ingestion of levorotatory; and the question has still to be decided whether in such cases the levorotatory sugar has been directly converted into dextrorotatory, or whether it has merely exercised in the body a sparing influence on the latter.

This limitation of the power in diabetics to utilize levorotatory sugar only is no isolated phenomenon in animate nature. Certain fungi and bacteria act in the same way as the cells.[2] Of the optically inactive lactic acid, which contains equal

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[1] J. B. Haycraft, *Zeitschr. f. physiol. Chem.*, vol. xix. p. 137: 1884; P. Palma, *Zeitschr. f. Heilk.*, vol. xv.: 1894; W. Hale White, *Zeitschr. f. klin. Med.*, vol. xxvi. p. 332: 1894; Karl Grube, *ibid.*, vol. xxvi. p. 340: 1894; C. A. Socin, "Wie verhalten sich Diabetiker Lävulose-Milchzuckerzufuhr gegenüber?" Dissert.: Strassburg, 1894. The earlier literature is here given.

[2] Pasteur, *Compt. rend.*, vol. xlvi. p. 615: 1858; vol. li. p. 298: 1860; vol. lvi. p. 416: 1863; J. A. Le Bel, *ibid.*, vol. lxxxvii. p. 213: 1878; vol. lxxxix. p. 312: 1879; vol. xcii. p. 843: 1881; J. Lewkowitsch, *Ber. d. deutsch. Chem. Ges.*, vol. xv. p. 1505: 1882; vol. xvi. pp. 1569, 2720, 2722: 1883. Also

quantities of dextrorotatory and levorotatory lactic acid, the *Penicillium glaucum* consumes the latter only, leaving the former untouched; in the same way, this fungus leaves the dextrorotatory only in a mixture of both kinds of mandelic acid. *Saccharomyces ellipsoideus*, on the contrary, consumes the dextrorotatory mandelic acid only, leaving the levorotatory; and this is also the case with a certain variety of bacterium. *Penicillium glaucum* behaves in the opposite way towards tartaric and glyceric acids compared with its action on lactic and mandelic acids; it leaves the levorotatory tartaric and glyceric acids untouched.

From the above remarks, it appears that so far we have only definitely ascertained that the power of utilizing dextrorotatory sugar is diminished in diabetes.

Now, as the bulk of the sugar is normally decomposed in the muscles, it seems probable that diabetes may fundamentally be due to a disturbance of the chemical processes in muscle.

Insufficient use of the muscles, a sedentary mode of life, are frequently given as causes of diabetes. This harmonizes with the fact that the disease comparatively often (30 per cent. of all cases) occurs in stout people. Obesity is invariably a result of insufficient muscular exertion (see end of Lecture XXIV.). Moveover, a few cases of diabetes have been successfully treated by systematic muscular exercise.[1]

But the chemical processes in muscle are subject to the influence of the nervous system, and numerous observations tend to show that the symptoms in diabetes are caused by disturbances which originate in the central nervous system. The disease sometimes occurs immediately after and may be traced to, injury to the head, or it accompanies organic affections of the brain (hemorrhages, tumors, sclerosis), or other nervous diseases, psychoses, &c. Occasionally violent mental excitement or neuralgia has caused an outbreak of the malady. In post-mortem examinations of diabetics, the brain more frequently shows pathological changes than any other organ.

Seegen,[2] who has treated over a thousand cases of diabetes, declares that 90 out of every 100 of such cases suffer from some form of nervous disorder, and adds that, in the numerous cases of hereditary diabetes in one and the same family, some may suffer from some form of psychical disorder, in most cases

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Em. Bourquelot, *Compt. rend.*, vol. c. pp. 1404, 1466; vol. ci. pp. 68, 958: 1885; Maumené, *ibid.*, vol. c. p. 1505; vol. ci. p. 695: 1885; H. Leplay, vol. ci. p. 479: 1885.

[1] Külz, *loc. cit.*, vol. i. pp. 179–216; and vol. ii. pp. 177–180.

[2] J. Seegen, "Die Zuckerbildung im Thierkörper, &c.," p. 263: Berlin, 1890.

melancholia leading off into suicide, while other members are diabetic.

Much confusion has arisen owing to the endeavor to explain the nature of chronic or 'natural' diabetes (as it has been called), from the observations carried out on 'artificial' diabetes. Cl. Bernard has shown that a puncture in the floor of the fourth ventricle, midway between the origins of the auditory and pneumogastric nerves, is followed by the passage of sugar into the urine. This artificial diabetes is obviously quite a different process to the natural disease. It lasts only for a few hours; and if, at the expiration of this time, when the urine has again become free from sugar, the animal be killed, no glycogen will be found in the liver. If all glycogen be removed from a dog by starvation, puncture of the 'diabetic center' remains without effect.[1]

If a solution of grape-sugar be injected into the mesenteric vein of a healthy dog, which has been deprived of glycogen by starvation, very little sugar appears in the urine. But if the liver be freed from glycogen by puncture of the floor of the fourth ventricle, and the injection into the mesenteric vein be then given, a very large amount of sugar is found in the urine.[2]

Artificial diabetes therefore is due to the inability of the liver, in consequence of disturbed innervation, to retain the glycogen. The blood becomes flooded with sugar, which passes into the urine.

If natural diabetes were due to the same cause, and if the liver had lost its power of regulating the amount of sugar in the blood, of storing carbohydrates during absorption, and of supplying sugar to the blood according to the needs of the economy, we should expect to find that the amount of sugar in the blood of diabetics would sometimes be above and sometimes below normal. This is not the case; it has always been found to be increased.

The objection may be raised that the diabetic patient takes food in such quantities and so often, that absorption is never interrupted, and that the blood is constantly loaded with sugar.

We must therefore try to decide the question in a direct

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[1] Leopold Seelig, "Vergleichende Untersuchungen über den Zuckerverbrauch im diabetischen und nicht diabetischen Thiere," Dissert.: Königsberg, 1873. The works of Pavy and Dock are quoted here. Luchsinger has published a confirmation of these results: "Exper. u. krit. Beiträge zur Physiol. u. Pathol. des Glycogens," Dissert., p. 72: Zürich, 1875.

[2] Naunyn, *Arch. f. exper. Path. u. Pharm.*, vol. iii. p. 98: 1875. A critical account is here given of the earlier works on this point.

manner, and ascertain whether a diabetic liver contains glycogen. This method has actually been adopted.

Külz[1] examined the liver of a patient who suffered from the aggravated form of diabetes, and had been for a long time before his death restricted to a diet of meat. The patient had taken his last meal thirty-four hours before death, and had been moribund for twenty-eight hours. The post-mortem took place twelve hours after death. About the tenth part of the liver served for the determination of glycogen, and yielded roughly 0.7 grm. of glycogen. Külz estimated the amount of glycogen in the whole liver at from 10 to 15 grms. Besides this, it contained a large quantity of sugar, part of which also originated from the glycogen.[2] The amount of glycogen during life must therefore have been very considerable.

Von Mering[3] had the opportunity of examining the livers of four diabetics in Frerichs' wards. "Two of them, who died of phthisis, and who had no sugar in the urine eighteen and twenty hours before decease (although there had previously been a considerable amount), exhibited neither glycogen nor sugar in their livers, although in one case the post-mortem examination took place immediately after death. In the two other cases where the diabetics died suddenly, and the urine removed from the bladder after death was full of sugar, both glycogen and sugar were found in abundance."

M. Abeles[4] examined the organs in the bodies of five diabetics, in E. Ludwig's laboratory in Vienna. No glycogen was found in any of the organs examined in two cases, one of which had died of phthisis, and the other of prolonged furunculosis and metastatic purulent pericarditis. The remaining patients had died from diabetic coma. The organs were not examined for several hours after death. The liver was examined in two cases, and a little glycogen was found: 0.16 grm. and 0.59 grm. There was none of the muscles.

The liver of living diabetics has also been examined for glycogen in Frerichs' wards.[5] These experiments are so important that I will quote the passages, unfortunately very short, in which they are described.

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[1] Külz, Pflüger's *Arch.*, vol. xiii. p. 267: 1876. See also the older statements of Kühne, Virchow's *Arch.*, vol. xxxii. p. 543: 1865; and M. Jaffé, *ibid.*, vol. xxxvi. p. 20: 1866.

[2] To obtain an exact estimate of the glycogen, the liver must be immersed in boiling water directly after death, in order to stop the fermentative action by which the glycogen would otherwise be broken up.

[3] Von Mering, Pflüger's *Arch.*, vol. xiv. p. 284: 1877.

[4] M. Abeles, *Centralbl. f. d. med. Wissensch.*, p. 449: 1885.

[5] Frerichs, *loc. cit.*, p. 272. Also plates of the histological sections of the livers.

"Professor Ehrlich effected it by means of a fine trocar, which had been carefully disinfected, and which was inserted in the parenchyma of the liver. When the instrument was removed, sometimes a little blood only, but generally a few hepatic cells, either isolated or united in groups, were found in the tube; there was occasionally a somewhat larger piece of the liver, which was hardened in alcohol, and cut, after being imbedded in celloidon. In this way, we were able to examine the hepatic tissue during life in three cases. They had all, both healthy and diabetic, eaten heartily, especially of amylaceous food. The puncture was made from four and a half to five and a half hours after the meal.

"A considerable quantity of glycogen was found in the first case, that of a healthy man, addicted however to alcohol. The cells in the peripheral regions of the acini had undergone fatty degeneration, but contained glycogen as well.

"The second case was that of the diabetic Dn. The hepatic cells were almost free from glycogen, though a few showed a slightly brownish hue, denoting the presence of traces of this substance.

"In the third case, that of a diabetic woman, a tolerably large amount of glycogen was found in the hepatic cells. The distribution of glycogen was very unequal, parts containing but little alternating with others richly provided with it. Large granules of glycogen, which frequently filled almost the whole of the cells, were often found at the margin of the lobule. They did not however consist of pure glycogen, but mainly of a supporting subtance, as their yellowish color denoted. They could not be regarded as artificial products caused by the alcohol, as they occurred likewise in dried preparations. The nuclei were generally free from glycogen, although in one place glycogen appeared to be deposited round the nucleolus. This is very analogous to the deposits of starch round the nucleoli in plants.

"Examination of the dried preparations, which were obtained from repeated punctures, showed the same result, *i. e.*, absence of glycogen in case 2, and a moderate amount in case 3."

I think these facts also indicate that we cannot apply the term diabetes to one single malady; lesions similar to those which produce artificial diabetes, may also produce certain forms of the malady (and especially glycosuria from injury to the medulla oblongata), but by no means all.

The fact that no sugar passes into the urine in cases of extensive hepatic disease, in cirrhosis of the liver, and in phosphorus-poisoning, is very remarkable. Frerichs could not detect any sugar in the urine, even after large quantities of grape-sugar had been taken, in cases of cirrhosis of the liver, where a subsequent autopsy showed complete degeneration of that organ.[1] After administration of from 100 to 200 grms. of grape-sugar to patients suffering from phosphorus-poisoning in Frerichs' wards a small amount of it was traced in the urine in two cases, while in seventeen others the result was negative. No trace of sugar or glycogen was ever found in the liver in any case of phosphorus-poisoning, where fatty degeneration of that organ had set in.[2]

Diabetes is evidently not due only to a disturbance of the glycogenic function of the liver. As far as I know, the muscle of diabetics has only been examined for glycogen in two cases, and, as already stated, with a negative result.[3]

Although the artificial diabetes discovered by Bernard does not serve to explain the natural form of this disorder, another kind of artificial diabetes, which has been the subject of much research during the last few years, seems to bring us nearer to a solution of the problem—I mean the diabetes that follows the extirpation of the pancreas.

It was long ago pointed out that pathological alterations in the pancreas are frequently to be found in autopsies on diabetics. Frerichs[4] especially drew attention to this point, and showed that, in fifty-five fatal cases of diabetes, well-marked macroscopic changes in the pancreas were to be found in eleven of them. The experimental proof of the connection of the pancreas with diabetes could however only be given later, after surgical technique and especially the aseptic method had reached the state of perfection necessary for so serious an operation.

J. von Mering and O. Minkowski[5] have operated on more than fifty dogs, and have found that, in all cases without exception where the complete extirpation of the pancreas had been successfully carried out and the animals had survived more than twenty-four hours, well-marked and severe diabetes was produced with all its characteristic symptoms, such as great thirst, large appetite, polyuria, and rapid decline of strength.

[1] Frerichs, *loc. cit.*, p. 43.

[2] *Ibid.*, p. 45.

[3] Abeles, *loc. cit.*

[4] Frerichs, *loc. cit.*, pp. 144–183. See also the case-histories, pp. 238–248.

[5] J. von Mering and O. Minkowski, *Arch. f. exper. Path. u. Pharm.*, vol. xxvi. p. 371: 1890. Minkowski, *Berl. klin. Wochenschr.*, No. 5: 1892; and "Untersuch. üb. d. Diabetes mellitus nach Exs. d. Pankreas," Leipzig, 1893. In this latter work the rest of the literature on the subject is fairly fully given.

The excretion of sugar began in some cases four to six hours after the operation, in most cases somewhat later, often not until the next day. Within twenty-four to forty-eight hours, the glycosuria reached its highest point, the sugar amounting to between 5 and 11 per cent. of the urine, even before the animals had taken any food whatsoever. Even after seven days' starvation or exclusive meat diet, the sugar did not disappear from the urine. For instance in one dog weighing 8 kilos. on a plentiful diet of meat and bread, the daily excretion of sugar over a considerable time amounted to between 70 and 80 grms. In some cases large quantities of aceton, aceto-acetic acid, and oxybutyric acid also made their appearance in the urine. The sugar was also largely increased in the blood. In one case, on the sixth day after the operation, it amounted to 0.3 per cent.; in another case, on the twenty-seventh day, to 0.46 per cent.

The glycogen, all but minute traces, disappeared early from the organs. Dextrorotatory grape-sugar, administered with the food, reappeared without loss in the urine. Levorotatory sugar was in great part utilized, though a certain proportion was converted into dextrorotatory, and excreted by the kidneys.[1] On feeding with levorotatory sugar, glycogen was deposited in the liver and muscles.

These statements of Mering and Minkowski have been confirmed by many other authors, especially by Lépine[2] and Hédon.[3]

If we now attempt to explain the connection between the extirpation of the pancreas and diabetes, the idea naturally presents itself that under normal circumstances the sugar-forming food-stuffs are altered in some way in the intestine by the pancreatic juice, and that this alteration is a necessary preliminary to their destruction in the tissues. Thus absence of pancreatic secretion would leave the sugar undestroyed.

It is quite true that certain disorders of digestion occur after ablation of the pancreas. The examination of the feces of dogs after this operation shows that a large amount of fat, proteid, and starch escapes absorption. This will not however serve to explain the symptoms of diabetes, since simple ligature of the pancreatic duct is not followed by any diabetes. Moreover in many cases the larger portion of the gland has been excised, and only a

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[1] Minkowski, "Untersuch.," &c., p. 68. Compare Fr. Voit, *Zeitschr. f. Biol.*, vol. xxviii. p. 353, and vol. xxix. p. 147: 1892.

[2] Lépine, *Wien. Med. Presse*, Nos. 27–32: 1892. Here also most of Lépine's previous papers are quoted.

[3] Hédon, *Arch. d. Physiol.*: April, 1892. *Compt. rend.*, vol. cxii. p. 1027: 1891; and vol. cxv. p. 292: 1892.

small bit has been left free from all connection with the duodenum, and yet no glycosuria has been produced. If fact diabetes as a rule occurs only after complete extirpation of the gland. If only a minute portion of the gland be left, there results either no diabetes at all or only the milder form of this disorder, in which sugar disappears from the urine on a purely proteid diet or during starvation, to reappear after eating bread. If the extirpation is complete, the glycosuria persists, as I have already mentioned, in spite of long-continued inanition. We must conclude therefore that the responsible factor is not a disturbance in the intestinal functions, and that the gland, besides the formation of its secretion, must possess other functions, which are a necessary condition of normal sugar destruction in the body.

Before however we inquire into the nature of this function, we must deal with an obvious objection that has been raised to these experiments, viz., that the glycosuria is caused by the unavoidable damage to neighboring organs, especially the solar plexus, in the course of the operation. That this is not the case is shown by the fact that any portions of the gland may be removed piece by piece without the occurrence of glycosuria. Only when the remaining fragment of the gland is extirpated do symptoms of diabetes make their appearance. Destruction of the solar plexus without removal of the pancreas produces, not diabetes but only acetonuria and transient glycosuria.[1] Especially decisive is the following experiment. The lowest portion of the descending limb of the pancreas in the dog is not connected with the duodenum, but lies free in the mesentery. This piece of the gland can be separated so as to be freely movable, and attached only by a long pedicle containing its artery and vein. It can therefore be taken out of the abdominal cavity and be grafted under the skin near the opening in the abdominal wall, without in any way interfering with its blood-supply. When the animal has recovered from this operation, the abdominal wound is again opened, and the whole remaining portion of the gland extirpated, so that the animal has left only the small portion of gland under the skin of the abdomen. After this operation no diabetes occurs, and large quantities of carbohydrates may be given to the animal, without giving rise to glycosuria. The small subcutaneous bit of pancreas prevents the development of diabetes, which at once follows in all its intensity if this piece be removed. "It is thus possible in this way to produce diabetes in its severest form leading to the death of the animal by a small operation, which lasts only a few minutes and is accomplished without opening the peritoneal

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[1] Lustig, *Arch. per le scienze mediche*, vol. xiii. Fas. 2: 1889.

cavity, and in which there can be no suspicion of any kind of injury to adjoining important structures." This experiment has been several times successfully performed by Minkowski, and in every case with the same result.

There can be thus no doubt that the pancreas influences directly or indirectly the destruction of sugar, and that this influence is absolutely independent of processes which go on in the small intestine. We must therefore assume either that the sugar of the blood undergoes some changes in passing through the gland, which prepare the way for its further destruction, or that the gland gives off some substance to the blood and tissues, which enables directly or indirectly the destruction to take place in other organs of the body.

The former assumption is rendered improbable by the fact that only a small fraction of the whole blood passes through the gland, especially in the experiments where the presence of a tenth part of the whole gland has prevented the appearance of diabetes. Moreover, in experiments carried out in Stricker's laboratory[1] on the amounts of sugar in the blood flowing to and away from the gland, no difference could be found.

The second assumption seems therefore the only possible one, viz., that the gland gives off some substance which influences the process of sugar destruction. This influence might of course be very indirect. We might imagine for instance that the substance in question plays a part in the functions of certain portions of the central nervous system, and that the metabolism of the muscles, where the chief part of the sugar is destroyed, is influenced by these nerve-centers. Analogies for such an indirect process are not wanting, and I might remind my readers of the extensive disturbances in the functions of the central nervous system, which result from the extirpation of the thyroid gland, and which are prevented so long as a piece of the gland is left or is transplanted into the abdominal wall.[2] We should thus return to our previous hypothesis, viz., that disturbances in the functions of the central nervous system are the cause of diabetes.

I would however once more emphasize the fact that the various forms of diabetes may have different modes of causation, and we need not assume that a morbid affection of the pancreas is in all cases a necessary preliminary. Even if pathological changes could be detected in the pancreas in all

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[1] Pal., *Wien. klin. Wochenschr.*, No. 4: 1891.

[2] A. von Eiselsberg, *Wien. klin. Wochenschr.*, p. 81: 1892. Here the previous literature is also quoted.

cases of diabetes, they might just as well be the consequence as the cause of the nervous affections.

A careful microscopical investigation of the pancreas in all fatal cases of diabetes is much to be desired. Hitherto pathologists have for the most part been satisfied with a mere inspection of the organ.

The varying course and issue of the disease seem also to show that there are many different forms of diabetes.[1] We can find all stages between transient and symptomatic glycosuria on the one hand, and the chronic variety of diabetes on the other. We occasionally see that the milder forms of chronic diabetes are as completely cured as symptomatic glycosuria. In chronic diabetes, a temporary disappearance of glycosuria may, as we have already mentioned, be frequently induced by a withdrawal of carbohydrates from the food. If the patient takes active exercise, a considerable quantity of carbohydrates may be borne without a passage of sugar into the urine. In other cases again, the excretion of sugar continues, although the food may consist exclusively of proteid and fat. Slight forms of diabetes frequently become aggravated, and, apart from this, they are not exempt from fatal complications. The severe form also runs a varying course. It is sometimes acute, and death occurs after a few weeks, or it may be after a year or two; in others, it may not take place for from ten to twenty years. Ordinarily glycosuria is associated with polyuria, the daily amount of urine rising to as much as 12 liters, while the patients are tortured by continual thirst. On the other hand, sugar may appear in the urine without polyuria and increased thirst. Frerichs[2] has observed more than thirty cases in which the amount of urine did not exceed 1700 to 2000 cms., while the quantity of sugar rose from 4 to 6, and even 8 per cent. In rare cases, diabetes mellitus may pass into diabetes insipidus,[3] polyuria without glycosuria. In diabetes, death is caused by

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[1] Frdr. Albin Hoffmann has made an interesting attempt to classify and define the various forms of diabetes (*Verhandl. d. Congr. für inn. Med.*, p. 159: Fünfter Congress, Wiesbaden, 1886). Compare also Külz, *loc. cit.*, vol. i. p. 217; and vol. ii. p. 144.

[2] Frerichs, *loc. cit.*, p. 192.

[3] This shows that polyuria in diabetes mellitus is not a necessary consequence, at any rate not in all cases, of the glycosuria, but may be the result of a special nervous disturbance. Concerning diabetes insipidus, see Külz, "Beitr. zur Pathol. u. Therap. des Diabetes mellitus u. insipidus," vol. ii.: Marburg, 1875. The previous literature on diabetes insipidus is summarized, pp. 28–31, and particularly that dealing with the occurrence of inosit in the urine in this disease. *Vide* Külz, *Sitzungsber. d. Ges. z. Beförd. d. ges. Naturw. zu Marburg*, No. 4: 1876. For the chemical properties of inosit, see Maquesne, *Compt. rend.*, vol. civ. pp. 225, 297 and 1719: 1887.

various complications, such as simple marasmus, pulmonary phthisis, furunculosis or carbuncles, nephritis, &c., and is frequently ushered in by diabetic coma.

I will dwell upon these symptoms a little more fully, because recent researches afford a perfectly satisfactory chemical explanation of them. The abnormal constituents of the urine, to which I have already drawn attention, oxybutyric acid, aceto-acetic acid, and aceton, which may frequently be traced in small quantities during the earlier stages of the disease, become considerably increased in coma. We shall immediately see that the cerebral symptoms occur at the same time that these substances are produced.

A comatose condition certainly may occur towards the close of the disease, without these abnormal products of metabolism being formed, but in these cases the coma depends upon complications, such as acute cardiac insufficiency, cerebral hemorrhage, nephritis, and the like. But in most cases, the above-named substances are demonstrable in the urine in diabetic coma; and the majority of authors have attributed this variety of coma to their narcotic influence,[1] especially to that of aceton, which acts in this respect like alcohol, ether, and other members of this group. But more careful experiments showed that the narcotic action of aceton was not powerful enough to account for diabetic coma,[2] especially if it be considered that aceton arises from proteid, and that the amount of the latter decomposed is not sufficient to yield the quantity of aceton required to produce coma.

The action of aceton resembles that of ethyl alcohol, but is not quite as powerful. Aceton can be given to dogs in the proportion of 1 grm. for every kilogrm. of body weight without any effect. Doses of 4 grms. for every kgrm. cause symptoms of intoxication with marked motor disturbances, similar to those produced by ethyl alcohol. Eight grms. for every kgrm. is the fatal dose of aceton, and from 6 to 8 grms. that of ethyl alcohol.[3] In order therefore to poison a person weighing 70 kgrms., from 500 to 600 grms. must be taken. This amount could not possibly be formed from decomposing proteid.

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[1] A complete summary of all the literature on this subject is given by von Buhl, *Zeitschr. f. Biolog.*, vol. xvi. p. 413: 1880; and by Rudolf von Jaksch, "Ueber Acetonurie u. Diaceturie": Berlin, Hirschwald, 1885. Also Frerichs, *loc. cit.*, pp. 114–120.

[2] *Vide* Peter Albertoni, *Arch. f. exper. Path. u. Pharm.*, vol. xviii. p. 218: 1884 (from Schmiedeberg's laboratory). This includes a complete report of the numerous earlier experiments.

[3] Albertoni, *loc. cit.*, pp. 223, 224, 226.

That diabetic coma does not result from the narcotic action of aceton is further proved by the fact already stated, that the amount of aceton in the urine sometimes diminishes during the stage of coma, while there is an increase in its precursor, oxybutyric acid, which has no paralyzing influence on the brain.[1]

Stadelmann[2] and Minkowski[3] have however offered a satisfactory explanation of this condition. They refer it to a saturation of the alkalies in the blood by the products of incomplete combustion, which are of an acid nature like oxybutyric acid. The symptoms of diabetic coma are in fact similar to those observed by Fr. Walter[4] in animals, which he poisoned with mineral acids. When dilute hydrochloric acid was injected into the stomach of a rabbit, dyspnea occurred, the animal lost the power of motion, and died with all the signs of collapse. But if carbonate of soda were subcutaneously injected after the symptoms of poisoning had set in, the animals recovered. Walter estimated the carbonic acid in the blood of animals which had been poisoned with acids, and found only from 2 to 3 per cent. by volume. This, as I have shown in our remarks on the gases of the blood (p. 262), is the amount of carbonic acid which is simply dissolved in the blood. Consequently the blood of the poisoned animals contained no alkalies that could fix the carbonic acid, as they had been saturated with the hydrochloric acid.[5] It follows that the blood had been deprived of the carrier of the carbonic acid, which consequently accumulated in the brain, and produced the usual symptoms. Walter has also demonstrated, as I have mentioned, that the administration of acids increases the amount of ammonia in the urine. Very similar phenomena are observed in diabetic coma. The effect of hydrochloric acid in the experiments on animals is identical with that of oxybutyric acid in diabetic coma. Here also dyspnea is a symptom; the diabetic also shows an increase of ammonia in the urine, and this increase

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[1] Wolpe, "Unters. über die Oxybuttersäure des diabetischen Harnes," Dissert.: Königsberg, 1886; *Arch. f. exper. Path. u. Pharm.*, vol. xxi. p. 138: 1886; and O. Minkowski, *Mittheilungen aus der medicin. Klinik zu Königsberg*, vol. xvii. p. 443: 1883.

[2] E. Stadelmann, *Arch. f. exper. Path. u. Pharm.*, vol. xvii. p. 443: 1883.

[3] O. Minkowski, *loc. cit.*

[4] Fr. Walter, *Arch. f. exper. Path. u. Pharm.*, vol. vii. p. 148: 1877 (from Schmiedeberg's laboratory).

[5] Walter (*loc. cit.*) speaks of withdrawal of alkali, which has not been proved by his experiments. The alkalies that are saturated by the acid may remain in the blood as neutral salts, until the kidneys have excreted the acid, leaving the bases in the blood.

reaches the highest point in the stage of coma.[1] Minkowski has also determined the amount of carbonic acid in the blood of a comatose diabetic patient, and has only found a volume percentage of 3.3. The blood had been taken a short time before the death of a patient from his radial artery.[2] Blood taken from the dead body had a distinctly acid reaction, and contained large quantities of oxybutyric and sarcolactic acids.

Finally, I may be permitted to make a few remarks on the treatment of diabetics from the chemical point of view.

So long as the causes of the different forms of diabetes are unknown to us, there can be no question of a rational mode of cure. We can do nothing more than relieve the most painful symptoms.

It has been quite right to try and reduce the amount of undecomposed sugar in the body, not only because it is useless, but because its circulation induces disturbances in all the tissues, and because certain organs, especially the kidneys, are overworked, and a tormenting thirst is induced. On this ground, muscular work is strongly to be recommended. Külz,[3] as we have already remarked, has shown that in many cases muscular exertion materially diminishes the excretion of sugar. Bouchardat asserts that he has obtained permanent improvement in many cases by this method. It does not answer in all cases, a circumstance which also tends to prove the existence of different forms of diabetes.

If we desire to reduce the amount of carbohydates, we must be prepared with a substitute. A diet consisting exclusively of proteid is objectionable, because it gives rise to acetonuria, and increases the danger of coma. So long as the theory prevailed that diabetes consisted essentially in an inability to decompose the sugar, it was sought to introduce the products of decomposition with the food. But we are not acquainted with the intermediate products of the decomposition of sugar, and even if they were known to us, we could not replace the sugar by introducing them, because at the moment of decomposition kinetic energy is liberated, which is utilized in the performance of muscular and other functions. Never-

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[1] Minkowski, *loc. cit.*, p. 179.

[2] I must refer to the extremely interesting original work for the details of this experiment. It also contains important critical observations on recent literature of diabetes.

[3] Külz, *loc. cit.*, vol. i. pp. 179–216 (where the older statements of Trousseau and Bouchardat are quoted), and vol. ii. pp. 177–180. Also Dr. Carl Zimmer, "Die Muskeln eine Quelle, Muskelarbeit ein Heilmittel bei Diabetes": Karlsbad, 1880; and von Mering, *Verhandl. d. Congresses f. innere Medicin*, p. 171 : Wiesbaden, 1886.

theless, some physicians have thought that the daily administration of from 5 to 10 grms. of lactic acid would serve as a substitute for the 300 to 800 grms. of carbohydrates required by an adult ! Larger quantities of lactic acid cannot be given, because they would disturb the digestion.

Acting on an erroneous supposition of O. Schultzen,[1] who imagined glycerin to be one of the normal products of the decomposition of sugar, they have tried to replace sugar by glycerin. The latter has the advantage over lactic acid of its sweet taste, but only a very small quantity can be prescribed. After larger doses diarrhea occurs, and a part of the absorbed glycerin passes unaltered into the urine (*vide supra,* p. 362).[2] Glycerin should therefore be given in its natural form as fat.[3] Fats can be digested very well by diabetics (*vide supra,* p. 388), and are the best substitutes for the carbohydrates.[4]

Many attempts have been made lately to administer levorotatory sugar to diabetics. C. A. Socin,[5] however, as the result of a careful experiment, gives an emphatic warning against this treatment. He finds that in the mild form of diabetes the levorotatory sugar is at first destroyed, but the body rapidly loses this power. The same result is observed after the administration of small quantities of dextrorotatory sugar, for which, even in the mild form of the disease, patients soon lose their tolerance.

It is well known that essential improvement in the condition of diabetics, especially with regard to the elimination of sugar, is effected by the use of alkaline, and particularly of Carlsbad, water in the water-cures. It was thought that the increased alkalescence of the blood favored combustion (*vide supra,* p. 247). This explanation appears still more probable if we consider the abnormal acids which occur in the blood of diabetics. But it has been proved by direct experiments that the mere administration of carbonates of alkalies without the mode of

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[1] O. Schultzen, *Berliner klin. Wochenschr.*, No. 35 : 1872.

[2] To satisfy the sense of taste, saccharin has recently been introduced as a substitute for sugar. With regard to the experiences of its use, see E. Kohlschütter und M. Elsässer, *Arch. f. klin. Med.*, vol. xli. p. 178 : 1887; and the article "Saccharin," by T. Stevenson and L. C. Wooldridge, in the *Lancet*, November 17, 1888.

[3] Considerable variety and change of diet may be effected in the way of fats with fat fish, of which a number are easy of digestion, yolk of egg, fresh cream (one-half of its small production of milk-sugar being utilized by diabetics), almonds, nuts, cocoa, and olives.

[4] Pettenkofer and Voit, *Zeitschr. f. Biolog.*, vol. iii. p. 441 : 1867.

[5] C. A. Socin, "Wie verhalten sich Diabetiker," &c., Dissert., Strassburg : 1894.

life adopted at watering-places, does not diminish the excretion of sugar.[1]

So far the attempts to subdue diabetic coma by the injection of carbonate of soda into the blood have remained without any favorable results.[2] We cannot expect to obtain any real improvement from the addition of alkalies, because this mode of treatment deals only with the symptoms, and not with the cause of the disease.

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[1] Frerichs, *loc. cit.*, p. 263. Nencki and Sieber, *Journ. f. prakt. Chem.*, vol. xxvi. p. 33: 1882. Also Külz, *loc. cit.*, vol. i. 31; ii. 154. A summary of all the earlier literature will be found here.

[2] O. Minkowski, *Mittheilungen aus der medicinischen Klinik zu Königsberg, i. Pr.*, pp. 183–186: 1888.

LECTURE XXVII

INFECTION

The time-worn controversy as to the origin of infectious diseases, whether they are brought about by living organisms —the "contagium vivum," or simply by poisons, *i. e.*, definite chemical substances, has been finally settled by the unceasing labors of the last two or three decades in favor of the former alternative. We know that the various infectious diseases are due to the entry of different and definite bacteria into the tissues of our body.

Now however arises the further question: Are the symptoms of these diseases the result of the mechanical disturbances caused by the spread of the bacteria through the tissues, or have we to do with the poisonous products of metabolism? And the conviction is growing more and more clear that the latter theory is the right one.[1]

We may cite the following proofs in support of this contention:

1. In certain infectious diseases the pathogenic organisms do not penetrate into the internal organs, but remain in the superficial mucous membranes, as in the case of diphtheria, or in the surface of the wound, as in tetanus. And yet in all these maladies, a general intoxication ensues.
2. Certain pathogenic bacteria may be cultivated outside the body in artificial nutrient fluids. Such a fluid can then be completely freed from bacteria by filtration, and the filtrate, when injected into the body of a healthy animal, will produce symptoms of poisoning similar to those which would result if the bacteria themselves were inoculated. (*Vide infra.*)

The adherents of the theory of "living contagion" had now the same duty to perform which had previously fallen to the lot of its opponents, *i. e.*, of isolating the poisons, of preparing them as chemical entities, investigating their characteristics and studying their behavior towards the constituents of the tissues. The morphologist had done his part; the chemist must now intervene.

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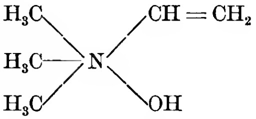
[1] An account of the earlier literature on this subject is given by P. L. Panum, *Virchow's Arch.*, vol. lx. p. 301: 1874.

The poison was first thought to belong to the nitrogenous organic bases, the alkaloids. This supposition was favored by the facts that the most intense organic poisons belong to the group of alkaloids, and that moreover nitrogenous bases may result from the metabolism of the bacteria. Poisonous bases readily arise from the decomposition of proteids, of the nucleins, or by a conversion of the nitrogenous bases preformed in the animal tissues, such as creatin, cholin, and the xanthin bodies.

The first attempt to isolate the poisonous bases produced by bacterial putrefaction was made by Bergmann and Schmiedeberg,[1] who prepared in a crystalline form the sulphate of an organic base from putrid yeast. When injected into a dog, 0.01 gr. of these crystals produced vomiting and bloody diarrhea.

Of the numerous and more recent experiments conducted with the object of isolating poisonous alkaloids from the bacterial products [2] I will only select those where a clearly defined chemical individual has been obtained, which has been proved to be acutely poisonous.

L. Brieger [3] prepared from putrid meat and fish two bases, which are closely allied to cholin and had probably been formed from the cholin which occurs in the form of lecithin in all animal tissues. One of these two bases was neurin; the other was isomeric with muscarin. (*Vide* Lect. VI. p. 76.) The neurin proved to be identical with that synthetically prepared by Hofmann [4] and von Baeyer,[5] which is distinguished from cholin by the possession of one less molecule of water. It must therefore be regarded as trimethyl-vinyl-ammonium hydroxid:



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[1] E. Bergmann and O. Schmiedeberg, *Centralbl. f. d. med. Wissensch.*, p. 497: 1868. Bergmann, *Deutsch. Zeitschr. f. Chirurgie*, vol. i. p. 373: 1872.

[2] The comprehensive literature on this subject is quoted by F. Gräbner, "Beitr. z. Kenntniss der Ptomaine," Diss., Dorpat: 1882. M. Nencki, *Journ. f. prakt. Chem.*, N. F., vol. xxvi. p. 47: 1882. L. Brieger, "Ueber Ptomaine," Berlin, Hirschwald, 1885. "Weitere Unt. üb. Ptomaine," 1885. "Unt. üb. Ptomaine." Dritter Theil, 1886, and *Virchow's Arch.*, vol. cxv. p. 483: 1889. Compare also F. Selmi, "Sulle ptomaine ed alcaloidi cadaverici e loro importanza in tossicologia," Bologna: 1878, and Gautier, "Cours de Chimie," "Chimie biologique," Paris, pp. 261–270: 1892.

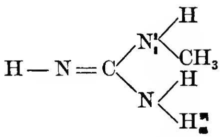
[3] L. Brieger, "Ueber Ptomaine," Berlin, Hirschwald, pp. 34–36 and p. 48: 1885.

[4] A. W. Hofmann, *Compt. rend.*, vol. xlvii. p. 558: 1858.

[5] Baeyer, *Ann. d. Chem. u. Pharm.*, vol. cxl. p. 311: 1866.

Both bases produced toxic effects similar to those of the muscarin prepared from fly-fungus. Besides the above-mentioned, Brieger[1] obtained from putrid meat, cheese and gelatin (in small quantity also from fresh eggs and fresh human brain), a base with the empirical composition $C_5H_{14}N_2$, the constitution of which could not be thoroughly ascertained. On boiling with potash it gave off dimethylamin and trimethylamin. Brieger gave it the name of neuridin. This base again produced in frogs and rabbits symptoms of poisoning similar to those caused by muscarin, and 2 mg. of the hydrochlorate of this base, when injected into the dorsal lymph-sac of a frog proved fatal. In rabbits the lethal dose was 0.04 g. per kilo. bodyweight.

Another base, methyl-guanidin, was isolated by Brieger[2] in small amounts from horse flesh which had been undergoing putrefaction for four months :



The poisonous character of this compound had already been remarked by Baumann and Gergens[3]: 1 mg. injected into the dorsal lymph-sac of a frog gave rise to definite toxic manifestations, consisting in fibrillar twitchings of the dorsal muscles; larger doses brought on convulsive movements of the extremities, which frequently became tetanic in character; 0.05 g. caused death, which occurred after the muscular symptoms had lasted for some time, occasionally for as much as three days. Brieger made a subcutaneous injection of 0.2 g. of methylguanidin prepared from putrid meat into a guinea-pig, which at once became paralyzed in the limbs and died twenty minutes afterwards with general clonic convulsions. We may assume that the methylguanidin was probably formed from the creatin of the meat. (See page 298.)

I shall not give any account of the numerous other bases, which have been isolated from bacterial products, since some of these (such as mydalein, typhotoxin, mydatoxin, gadinin, &c.) have not been obtained in a pure state, or if they have, in such small amounts that their chemical properties and

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[1] Brieger, *loc. cit.*, pp. 20–30, 51, 54, 57, 61.

[2] Brieger, "Unt. üb. Ptomaine," Dritter Theil, Berlin, 1886, p. 34, *et seq.* Compare Hoffa, *Sitzungsber. d. phys. med. Ges. zu Würzburg*, pp. 101 and 102 : 1889.

[3] Baumann and Gergens, Pflüger's *Arch.*, vol. xii. p. 205 : 1876.

physiological effects could not be properly tested. On the other hand others, such as methylamin, dimethylamin, trimethylamin, tetramethylendiamin (putrescin), pentamethylendiamin (cadaverin), &c., have been found to be quite innocuous. The investigation of the last-mentioned products forms a valuable contribution to the material for a future physiology of bacterial metabolism.[1] But so far it has added nothing to our knowledge of the etiology and symptoms of infectious diseases.

In the case of the poisonous bases, there is not always sufficient evidence that the poison is due to the bases themselves and not merely to the impurities in them. Researches up to the present seem to show that the more carefully the bases are purified, the less action do they have on the animal body. It is greatly to be desired that in future all investigation on the metabolic products of microörganisms should be confined to "pure cultures," both with the object of obtaining an insight into bacterial changes as well as for the purpose of increasing our knowledge of the etiology of infectious diseases. In this way it could always be definitely ascertained by which species of bacteria the material under examination was formed. Another point of great importance is that the chemical composition of the nutrient medium before the introduction of the bacteria should be accurately determined. A beginning to investigations of so exact but laborious a nature has already been made by Brieger,[2] Roux and Yersin,[3] Löffler,[4] Kitasato and Weyl,[5] Tizzoni and Cattani,[6] Nencki and his pupils, besides others.

If we now proceed to inquire whether the symptoms of infectious diseases may really be explained from the known toxic effects of the bases which have been isolated from the bacterial products, we must acknowledge at once that it is impossible to expect any absolute agreement. We may in-

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[1] To this group belongs also the compound isomeric with collidin, which Nencki prepared from putrid gelatin, and which was the first of the organic bases isolated from bacterial products. Nencki, "Ueb. die Zersetzung der Gelatine und des Eiweisses b. d. Fäulniss mit Pankreas," Festschrift, Bern. p. 17: 1876. See also S. Adeodato Garcia, *Zeitschr. f. physiolog. Chem.*, vol. xvii., pp. 543–595: 1893.

[2] Brieger, "Weitere Unt. üb. Ptomaine," Berlin, 1885, p. 67, *et seq.*, and "Unt üb. Ptomaine," Dritter Theil, p. 84, *et seq.*: 1886.

[3] E. Roux et A. Yersin, *Annales de l'Institut Pasteur*, Année ii., p. 642: 1888.

[4] F. Löffler, *Deutsch. med. Wochenschr.*, Jahrgang 16, p. 109: 1890.

[5] S. Kitasato u. Th. Weyl, *Zeitschr. f. Hygiene*, vol. viii. p. 404: 1890, and Kitasato, idem, vol. x. p. 267: 1891.

[6] Tizzoni u. Cattani, *Arch. f. exper. Path. u. Pharm.*, vol. xxvii. p. 432: 1890.

deed anticipate the direction in which the main differences will lie.

In the first place, the artificial production of the disease by the injection of a substance already prepared from the pathogenic microörganisms, does away with the first characteristic of all zymotic disease — that of incubation. If the infection is caused by the entrance of a small number of bacteria, a certain time must naturally elapse before these can increase and enter the circulation and the chief organs, to the disturbance of whose functions the salient symptoms of the disease are due. Whereas with the injection of a poison — especially of such a poison as the bases of a soluble salt — the disturbances must commence at once, and the whole series of symptoms must run a more rapid course. Further, we must not forget that the injected poison does not necessarily reach all the organs, tissues, and cells which the bacteria do, and that on the other hand, the bacteria may not enter all the parts where the poison may penetrate by diffusion. Finally, we must take into consideration that there is probably more than one poisonous product from each species of pathogenic microbes, and that the various symptoms of any given zymotic disease may be caused by different poisons, or by a combination of two or more poisons. The artificial injection of a chemical individual might not produce these identical symptoms.

But even when we have made every allowance for possible differences, it remains improbable that the alkaloids of putrefaction which have up to the present time been examined, are responsible for the symptoms of the various infectious diseases, for the reason that they are not nearly poisonous enough. We must remember that the body possesses in a marked degree the faculty of getting rid of injurious substances of all kinds as they are formed. In seeking an explanation for the symptoms of zymotic disease we may therefore restrict ourselves to the poisons of great virulence.

The toxic action of the alkaloids of putrefaction, of the so-called ptomains and toxins, has been much exaggerated, because small animals, and especially mice, were used for the experiments. Now we must not forget that the bodyweight of a mouse is only about 10–17 g. If for example we take tetanin — a base which was first isolated by Brieger from the metabolic products of the tetanus bacilli, and considered to be the specific tetanus poison — we find that 3 cg. of the hydrochlorate is necessary to kill a mouse when subcutaneously injected, *i. e.*, 2–3 g. per kilo. bodyweight. In the case of a guinea-pig (about $\frac{1}{2}$ kilo.) 0.5 g. (therefore 1 g. per kilo.) had "but little effect" subcutaneously; the animal did not succumb.[1] Whereas, according to Tizzoni and Cattani,[2] $\frac{1}{10}$th drop of the tetanus cuture filtrate, *i. e.*, of the nutrient fluid from which the tetanus bacilli had been entirely removed by filtration, was sufficient to cause the death of medium-sized rabbits from tetanus. Vaillard and Vincent[3] state that 1 ccm. of the filtered culture of the tetanus bacilli in broth contained only 0.025 g. organic matter, and that this amount — of which the poison formed but a fraction — was enough to kill a thousand guinea-pigs, or a hundred thousand mice!

Similar observations have also been made with other pure cultivations of pathogenic bacteria. The fluids in which the bacteria have lived contain poisons of far greater virulence than the alkaloids which have been isolated from them.

Ceaseless endeavors have during the last few years been made to investigate these powerful poisons. Here again the same difficulties were met with as in the attempt to isolate ferments (*vide* Lecture XI. p. 159). The toxic substances cannot be separated from certain proteids. The first author, who came to the conclusion that the poison produced by the bacteria "clung to the proteids" was Panum.[4] He says: "It almost seems as if, led away by the desire to find a crystallized body, the investigator had overlooked the fact that impurities with crystallized foreign substances are as much impurities as the presence of substances which prevent the crystallization of a body.[5]

Roux and Yersin[6] filtered broth cultivations of diphtheria bacilli through clay cells: the filtrate was still effective, 2 cm. killing a rabbit when injected subcutaneously. But it proved inoperative after being heated for ten minutes to 100° C.: 35 ccm. could be injected directly into the vein of a rabbit without any injurious consequences. These authors therefore imagine that the active constituent might be of a nature similar to that of the hydrolytic ferments. In common with the ferments, it likewise possessed the property of being carried

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[1] S. Kitasato u. Th. Weyl, *Zeitschr. f. Hygiene*, vol. viii. p. 407: 1890.

[2] Tizzoni u. Cattani, *Arch. f. exper. Path. u. Pharm.*, vol. xxvii. p. 437: 1890. Compare also S. Kitasato, *Zeitschr. f. Hygiene*, vol. x. p. 267: 1891.

[3] Vaillard et Vincent, *Annales de l'Institut Pasteur*, Ann. V. p. 15: 1891.

[4] Panum, "Bibliothek for Laeger," vol. viii. pp. 253–285: 1856. Summarized in Schmidt's Jahrb., pp. 213–217: 1859; and *Virchow's Arch.*, vol. lx. p. 334: 1874.

[5] *Virchow's Arch.*, vol. lx. p. 332: 1874.

[6] E. Roux et A. Yersin, *Ann. de l'Institut Pasteur*, Année II. p. 642: 1888; and Année III. p. 273: 1889. Compare S. Dzierzgowski et L. de Rekowski, *Arch. d. Sciences Biolog.*, publ. par l'Institut impérial de Méd. exp. à St. Petersbourg, vol. i. p. 167: 1892.

down by neutral precipitates such as phosphate of lime. Subcutaneous injection of 0.02 g. of such a moist precipitate, containing less than 0.0002 g. of organic substance, killed a guinea-pig in the space of four days. The poison, although capable of being dialyzed, has no effect when taken into the stomach.

Löffler[1] was able to obtain the active toxic principle from meat-broth in which a pure culture of diphtheria bacilli had been made, by the same method usually employed for isolating ferments: *i. e.*, extraction with glycerin and precipitation with alcohol. The poison thus obtained, when injected subcutaneously into guinea-pigs, occasioned the same local symptoms as did the inoculation with the bacilli themselves.

L. Brieger and C. Fränkel[2] made similar experiments with cultures of diphtheria, typhus, tetanus, and cholera bacteria, with staphylococcus aureus, with watery extracts from the organs of animals which had died of anthrax. They invariably found that the toxic properties were associated with certain proteid precipitates, which were thrown down on the addition of alcohol or of a concentrated solution of ammonium sulphate. If heated above 60° C. the substances were rendered innocuous, although they withstood evaporation to dryness at 50°.

Wassermann and Proskauer[3] repeated these experiments of Brieger and Fränkel, and prepared proteid precipitates from the filtrates from pure cultivations of diphtheria bacilli. About 10 mg. of such a precipitate injected under the skin killed a rabbit in about 3 to 4 days.

Tizzoni and Cattani[4] precipitated a proteid with sulphate of ammonia from the filtrate of pure cultivations of tetanus bacilli. 4 mg. of this proteid precipitate injected subcutaneously killed a rabbit weighing 2 kg. with "all the signs of tetanus."

From filtered cultures of the same bacillus, Vaillard and Vincent[5] also obtained a proteid, which was either thrown down from watery solutions by alcohol, or was carried down by neutral precipitates such as phosphate of lime. This proteid, however was less poisonous than the filtrate of the pure

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[1] Löffler, *Deutsch. med. Wochenschr.*, Jahrg. 16, p. 109: 1890.

[2] L. Brieger and C. Fränkel, *Berlin. klin. Wochenschr.*, Jahrg. 27, pp. 241 and 268: 1890.

[3] A. Wassermann and B. Proskauer, *Deutsch. med. Wochenschr.*, Jahrg. 17, p. 585: 1891.

[4] Tizzoni and Cattani, *Arch. f. exper. Path. u. Pharm.*, vol. xxvii. p. 447: 1890.

[5] L. Vaillard and H. Vincent, *Ann. d. l'Institut Pasteur*, Année V. pp. 15, 19–20: 1891.

cultures from which it was prepared. Of the latter an amount containing only 0.000025 g. of organic substance sufficed to kill a guinea-pig, whereas it took 0.00015 g., or six times more of the proteid precipitate, to produce the same effect.[1] In the various procedures adopted for isolating the toxin therefore it has become partially destroyed. Kitasato was likewise unsuccessful in obtaining a precipitate which was more poisonous than the filtered cultures from which he started. Here again we have an analogy with the hydrolytic ferments. Fresh gastric and pancreatic juices or freshly prepared extracts from the gastric mucous membrane or pancreas are always more active than the ferments isolated from them. The poisonous products of bacteria are therefore, like the hydrolytic ferments, extremely labile compounds. The same observation was made by Wassermann and Proskauer.[2]

Among the products excreted by the tubercle bacillus there is likewise a substance which is precipitated by alcohol or by a concentrated solution of ammonium sulphate and dissolves again in water. On addition of acetic acid and sodium chlorid to the watery solution, a precipitate is thrown down which disappears on heating. The substance is diffusible; it is soluble in glycerin, and may be precipitated from this solution by alcohol. The toxic effect is connected with this substance which, to judge from its reactions, belongs to the precursors of proteid, the so-called albumoses. The subcutaneous injection of a small amount (about 1 mg.) into a healthy person caused a rise of temperature to 39.1° C.; in a woman suffering from lupus, an amount five times less produced a rise to 40.4° C.[3]

From a pure cultivation of streptococcus pyogenes, N. Sieber[4] obtained an albumose precipitate, of which 0.013 g. injected under the skin of a rabbit caused the temperature to run up to 39.2–40.6°.

From all these facts it is evident that the most virulent products of bacterial metabolism are either proteids or substances which have solubilities similar to those of the proteids, and hence are precipitated with them. Most authors who have worked on this subject adopt the former view, and therefore call these poisonous substances TOXALBUMINS.

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[1] S. Kitasato, *Zeitschr. f. Hygiene*, vol. x. p. 296: 1891.

[2] *Loc. cit.*

[3] R. Koch, *Deutsch. med. Wochenschr.*, No. 3, and No. 43: 1891. Martin Hahn (Nencki's Laboratory), *Berl. klin. Wochenschr.*, No. 30: 1891. The earlier work on tubercle toxin is here quoted. Compare M. C. Helman, *Arch. d. sciences biol.*, publ. par l'Institut imp. de Méd. exp. à St. Petersbourg, vol. i. p. 139: 1892. O. Bujwid, *idem*, p. 213, and W. Kühne, *Zeitschr. f. Biol.*, vol. xxix. p. 24: 1892, and vol. xxx. p. 221: 1893.

[4] N. Sieber, *Arch. d. sciences biol.*, vol. i. p. 285: 1892.

The toxalbumins are not exclusively confined to bacterial products, but have been also found to exist in the animal and vegetable kingdoms. Thus all recent workers[1] on the poisonous secretion of snakes have come to the conclusion that the active toxic principles belong to the group of proteids. The poison contained in the blood-serum of the muranids is shown by Mosso[2] to be of the same nature as snake-poison. This author considers that this substance is probably a proteid, an opinion likewise held by Kobert concerning the poison of spiders.[3] The large spider, *Lathrodectes tredecimguttatus*, which occurs in the south of Russia, contains poison in all parts of its body, even in its legs and undeveloped eggs. If this poison be introduced directly into the blood, its effect is more potent than strychnin or hydrocyanic acid, although it has no action in the stomach, and is destroyed on boiling.

The toxalbumins again are distributed over the vegetable kingdom. To this class apparently belong the intensely poisonous constituents of the jequirity seed[4] (*Abrus precatorius*), and that of *Ricinus communis*[5] as well as the poison of a fungus, the *Amanita phalloides*,[6] all of which resemble the toxalbumins in their chemical and physical behavior. If injected intravenously, 0.5 mg. per kilo. bodyweight is sufficent to cause death in the case of the poisonous principle of the *Amanita phalloides*, and 0.01–0.02 in the case of that of the jequirity seed.[7]

As the toxalbumins and the hydrolytic ferments, the so-called enzymes, present the same conditions of solubility, besides possessing many other chemical qualities in common,

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[1] R. Norris Wolfenden, *Journ. of Physiol.*, vol. vii. pp. 327 and 357: 1886. S. Weir Mitchell and Edward Reichert, "Researches upon the Venoms of Poisonous Serpents." Smithsonian Contributions to Knowledge, 647, p. 186: Washington, 1886. Brieger and Fränkel, *Berl. klin. Wochenschr.*, Jahrg. 27, p. 271: 1890.

[2] A. Mosso, *Acad. dei Lincei*, vol. iv. p. 665: 1885; and *Arch. f. exper. Path. u. Pharm.*, vol. xxv. p. 111: 1889. U. Mosso, *Rendiconti della r. Acad. dei Lincei*, p. 804: 1889.

[3] Kobert, *Sitzungsber. d. Naturforscher-Gesellsch. zu Dorpat*, vol. viii. pp. 362 and 440: 1889.

[4] Sidney Martin and R. Norris Wolfenden, *Proc. Roy. Soc.*, London, vol. xlvi. pp. 94 and 100: 1889. Sophie Glinka, "Beitr. z. Kenntniss d. giftigen Princips d. Jequiritysamen," Diss., Bern.: 1891. The earlier literature is here quoted. Nencki, *Schweizer Wochenschr. f. Pharmacie*, No. 29: 1891. Reprint, p. 5, Heinr. Hellin, "Der giftige Eisweisskörper Abrin.," Diss., Dorpat: 1891. P. Ehrlich, *Deutsch. med. Wochenschr.*, No. 44: 1891.

[5] H. Stillmark, "Ueber Ricin," Diss., Dorpat: 1888. P. Ehrlich, *Deutsch. med. Wochenschr.*, No. 32: 1891.

[6] Kobert, *Sitzungsber. d. Nat. Ges. zu Dorpat*, vol. ix. p. 541 *et seq.*: 1891. This author gives a summary of our present knowledge concerning the various poisons in the different fungi.

[7] Kobert, *idem*, vol. ix. pp. 116 and 553: 1891.

it was fair to assume that they also shared the same poisonous properties. Roussy[1] found that intravenous injection of invertin in dogs gave rise to fever, less than ½ mg. to 1 kilo. body-weight being sufficient to cause a rise of temperature to 42° C. H. Hildebrandt[2] showed that the subcutaneous injection of larger quantities (0.1 g.) of pepsin, invertin, diastase, was fatal to medium-sized rabbits, the animals succumbing in 2 to 4 days. After doses of between 0.05 and 0.1 g. the animals did not die until after the lapse of one or more weeks. With emulsin and myrosin a dose of 0.05 g. was always fatal in 2 to 4 days. In dogs relatively larger amounts of pepsin and invertin (0.1 to 0.2 g. per kilo.) were required to cause death. In all the experiments there was a rise of temperature amounting on the average to 2° C.

We might now ask: If the hydrolytic ferments have a toxic action, might not the toxalbumins have an hydrolytic action, and perhaps by this very means develop their poisonous properties in the tissues? This does not however appear to be the case. Direct experiment has shown that the diphtheria and tetanus toxins do not act hydrolytically.[3]

It has frequently been stated that certain products of artificial proteid digestion, certain peptones and their precursors, the so-called albumoses, have a poisonous action.[4] This action is only produced on direct introduction of these substances into the blood, probably for the reason that in the passage through the intestinal wall the peptones are reconverted into proteids. But even in the former case the toxic effects—narcosis and lowering of the blood-pressure—are only brought about by very large doses—0.3 g. per kilo. body-weight. The poison is therefore not of a violent nature. It is possible that both with these digestive products of the proteids as well as with the enzymes, the toxic effect is to be ascribed to an admixture of toxalbumins arising from bacterial metabolism. It is highly desirable that the experiments should be repeated with absolutely sterilized material under strict antiseptic precautions.

In the foregoing remarks we have enumerated the various

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[1] Roussy, *Gaz. des Hôp.*, No. 19 and No. 31: 1891. Compare the appreciation of this work presented to the Acad. by Schützenberger, Gautier, and Hayem: *Bull. d. l'Acad. de Méd.*, Série 3, vol. xxii. p. 468: 1889.

[2] H. Hildebrandt, *Virchow's Arch.*, vol. cxxi. p. 1: 1890.

[3] L. Vaillard and H. Vincent, *Annales d. l'Institut Pasteur*, Ann. 5, p. 20: 1891.

[4] Schmidt-Mülheim, *Du Bois' Arch.*, pp. 50–54: 1880. Fano, *idem*, p. 277: 1881. W. Kühne and Pollitzer, *Verhandl. d. nat.-med. Vereins zu Heidelberg*, N. F., vol. iii. p. 292: 1886. R. Neumeister, *Zeitschr. f. Biol.*, N. F., vol. vi. p. 284: 1888.

properties which the toxalbumins and the enzymes have in common. There are however differences not only between the toxalbumins and the enzymes but among the toxalbumins themselves. A few of the latter are, like the globulins, insoluble in water, as for instance the poisonous proteid precipitates obtained from cultures of typhus bacilli and staphylococcus pyogenes aureus. Most of the toxalbumins however are, like the ferments, soluble in water, but not dialyzable. An exception to this is formed by the poison of the rattlesnake,[1] as well as of the tubercle bacillus, both of which are dialyzable. Tetanus and diphtheria poisons dialyze slowly.

A temperature of over 50° C. causes many of the solutions of toxalbumin to lose their virulence; but there are some which will stand heating to 60° and higher, or even for a short time to 100° C., as for instance the poison of the Indian cobra and the toxalbumin of the tubercle bacillus. We may assume perhaps that the toxalbumins which are rendered innocuous by boiling belong to the proteids properly so-called, whereas those which are not affected by this temperature may be referred to the peptons.[2] If this assumption be correct, we should expect to find that the toxalbumins which are not affected by boiling are dialyzable. This is the case with tubercle. When in a dry condition the toxalbumins, like the ferments, can be raised to a high temperature (*e. g.*, certain snake poisons to 115° C.) without losing their virulence.

Absolute alcohol has no effect on some of the toxalbumins, *e. g.*, the snake-poison, but others again it gradually renders ineffective. Thus, according to Kitasato, the tetanus poison loses its power if it be exposed to the action of 70 per cent. ethyl alcohol for one hour or to that of 60 per cent. for twenty-four hours.

Alkalies and acids weaken or destroy the operation of many toxalbumins. The poisonous effect of snake-venom is diminished by alkalies. Tetanus poison is destroyed by free alkalies: a 0.3 per cent. solution of sodium hydrate, or a 3.7 per cent. solution of sodium carbonate will accomplish this in an hour; a 1 per cent. solution of ammonia must be allowed twenty-four hours. Again, a solution of 0.365 per cent. hydrochloric acid will take twenty-four hours, and one of 0.55 per cent. one hour to destroy the tetanus poison. The toxin of muranids is

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[1] W. Heidenschild, "Unt üb. d. Wirkung d. Giftes d. Brillen- u. Klapperschlange," Diss., Dorpat: 1886.

[2] S. Weir Mitchell and E. T. Reichert, *loc. cit.*

deprived of its activity by the action of acetic or hydrochloric acid, or by that of gastric juice. If however the poisonous serum be injected through the abdominal wall into the small intestine, death ensues. I mentioned above that the poison of spiders as well as the tubercle and tetanus toxins were innocuous when introduced into the stomach.

Before leaving the consideration of the toxalbumins, I must mention one observation which may perhaps have a very wide bearing. Of late years many communications have been made concerning the existence in normal blood of proteids which behave towards certain bacteria like toxalbumins. An attempt has been made to explain the phenomena of immunity in this way, but the data are not yet sufficiently precise to permit of a connected account.[1]

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[1] For a summary of the literature on this subject see R. Stern, *Zeitschr. f. klin. Med.*, vol. xviii. p. 46: 1891. Compare also the Address given at the 11th Congress for Clinical Medicine at Leipzig by H. Buchner, and printed in the *Berl. klin. Wochenschr.*, No. 19: 1892: and H. Buchner, *Arch. f. Hygiene*, vol. xvii. pp. 112, 138: 1893; G. Tizzoni u. J. Cattani, *Berl. klin. Wochenschr.*, Nos. 49–52: 1893; and Nos. 3: 1894; M. Hahn, "Ueb. d. Beziehungen d. Leukocyten z. bactericiden Wirkung d. Blutes," Pro venia legendi, München: 1895.

LECTURE XXVIII

FEVER

Almost all forms of infection lead to the complex of symptoms which we term fever. Of these symptoms the rise of temperature is, as we know, the most readily measured and has therefore been the subject of the most thorough investigation. Teleologically this rise of temperature may be explained on the assumption that by its means the pathogenic microörganisms are killed, or at least arrested in their development, and their pathogenic properties weakened.

Thus Heydenreich[1] observed that the spirilla of recurrent fever lost their mobility much more readily at 40° C. than at 70° C. According to R. Koch[2] the most favorable temperature for the tubercle bacillus lies between 37° and 38° C. When kept at 42° C. for three weeks, its further development is impeded. For the gonococcus-Neisser the optimum temperature is between 33° and 37 C.[3] A temperature of 39° C. kills it in twenty-four hours, and one of 42° in twelve hours.[4] De Simone[5] found that the multiplication of the streptococcus erysipelatosus stopped entirely at 39° to 40° C., and that the organism died at 39.5° to 41° C. Bard and Aubert[6] found that of the medley of bacteria in the feces, all of them disappeared, with the exception of the bacillus coli communis, under the prolonged action of fever temperature. According to Fränkel[7] the virulence of the septicemic cocci of the sputum is entirely abolished by growing it for two days at 42° C., or for four to five days at 41° C. Pasteur[8] discovered that anthrax bacilli,

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[1] Heydenreich, *Centralbl. f. d. med. Wissensch.*, No. 28 : 1876.

[2] R. Koch, "Zur Aetiologie der Tuberculose," *Mitth. a. d. kais. Gesundkeitsamte*, vol. ii.: 1894.

[3] Bumm, "Der Micro-organismus d. gonorrhoischen Schleimhauterkrankung Gonococcus-Neisser," Wiesbaden : 1887.

[4] Finger, *Verh. d. deutsch. Dermatolog. Ges.*, IV. Congress, p. 181 : 1894.

[5] Fr. de Simone, Il Morgagni, Nos. 8–12 : 1885.

[6] L. Bard and P. Aubert, *Gaz. hebdom. d. Méd. et de Chirurg.*, No. 35, p. 418 : 1891.

[7] A. Fränkel, *Zeitschr. f. klin. Med.*, vol. x. Hft. 5 and 6 : 1886.

[8] Pasteur in collaboration with Chamberlain and Roux, *Comptes rend.*, vol. xcii. pp. 422, 662, 666, and 1379: 1881. Compare R. Koch, "Zur Aetiol. d.

after being exposed for some time to a temperature of 42° to 43° C., lost their pathogenic character, and that animals when inoculated with the bacilli in this condition became immune to the actual disease. G. and F. Klemperer[1] heated broth-cultures of pneumococci for two to three days to 41° to 42° C., and found that when they were injected into rabbits the latter were rendered immune to the infection of pneumococci.

These results not only explain the significance of fever but also indicate how immunity may occur after infectious diseases. In this connection we must remember that in fever the average temperatures only are taken, and it is quite possible that in certain tissues, and perhaps more especially in those parts where the bacteria most abound, the temperature runs up to a much higher level. The rise of temperature in fever would therefore be one of the processes of self-protection and self-regulation, of which we have so many examples in the body.[2] This view concerning the significance of fever temperatures is not contradicted by the fact that some of the pathogenic organisms are able to withstand considerable rise of temperature. For instance the temperature of 42° C. does not kill the typhoid bacillus, and only slightly impedes its rate of propagation. The typhoid bacilli must be exposed to a temperature of about 44.5° C. for a considerable time before any appreciable number are killed.[3]

With regard to the mechanism by which the rise of temperature is brought about, it was first considered that it was probably due to an increased metabolism. Alfred Vogel,[4] adopting Liebig's titration method in 1854, found that the nitrogenous excretion was augmented in cases of febrile diseases. This

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Milzbrandes," *Mitth. a. d. kais. Gesundheitsamt.*, vol. i.: 1881; and Arloing, "Les virus," Paris: 1896.

[1] G. and F. Klemperer, *Berl. klin Wochenschr.*, Nos. 34 and 35: 1891.

[2] If this interpretation of the significance of fever be correct, the treatment of febrile disorders by means of cold baths and antipyretic remedies would appear to be a bad one. For information on these debated questions the following articles may be recommended: Unverricht, *Deutsch. med. Wochenschr.*, Jahrg, 13, pp. 452 and 478: 1887; and Jahrg. 14, pp. 749 and 778: 188; Liebermeister, *idem*, vol. xiv. pp. 1 and 26: 1888; Naunyn, *Arch. f. exper. Path. u. Pharm.*. vol. xviii. p. 49: 1884; Arnaldo Cantani, "Ueb. Antipyrese," Vortrag, *Verhandl. d. X. internat. med. Congresses*, Berlin, Hirschwald, p. 152: 1891. A critical account of the literature on the action of the antipyretic remedies is given by Gottlieb, *Arch. f. exper. Path. u. Pharm.*, vol. xxvi. p. 419: 1890; vol. xxviii. p. 167: 1891. Compare also A. Loewy and P. F. Richter, *Deutsch. med. Wochenschr.*, No. 15, p. 240: 1895; and *Virchow's Arch.*, vol. cxlv. p. 49: 1896.

[3] Max Müller, "Ueb. d. Einfl. v. Fiebertemp. a. d. Wachsthumgeschwindigkeit u. d. Virulenz d. Typhus bacillus," Diss., Breslau: 1895; reprinted from the *Zeitschr. f. Hygiene u. Infectionskrankheiten*, vol. xx.

[4] A. Vogel, *Zeitschr. f. ration. Med.*, N.F., vol. iv. p. 362: 1854; and "Klinische Unt. ü. d. Typhus," Erlangen: 1860.

statement was subsequently confirmed by many observers.[1] At the same time elimination of the sulphuric acid is correspondingly increased, as might have been expected.[2]

Liebermeister[3] and Leyden[4] found that the output of CO_2 was also increased in fever. These observations on man were confirmed by experiments on animals carried out by different observers,[5] and it was moreover ascertained that an increased amount of oxygen was taken in as well as a larger amount of carbonic acid eliminated.[6]

It is however doubtful whether this heightened metabolism is the cause of the rise in temperature. In the first place, we know that in a normal person a very considerable increase in metabolism may occur (*e. g.*, in strenuous muscular work) without any rise of temperature, since the body possesses various means of compensating for the increased heat production by increasing the heat loss. In the second place, the metabolism is not quickened in all fevers. Numerous experiments on man and on animals have shown that in some cases of fever the intake of oxygen and the output of carbonic acid remains the same or is even less than normal.[7]

The rise of temperature must therefore have some other cause than merely the increase of metabolism. There is only one other theory left, *i. e.*, that there is less heat given off. This idea was warmly supported by L. Traube,[8] who taught that

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[1] An account of the comprehensive literature is given by Senator, "Unt. üb. d. fieberhaften Process," Berlin, 1873, p. 94 *et seq.;* and by Naunyn, *Arch. f. exper. Path. u. Pharm.*, vol. xxviii. p. 49: 1884. Compare also L. Riess, *Virchow's Arch.*, vol. xxii. p. 127: 1886; Hirschfeld, *Berl. klin. Wochenschr.*, No. 2: 1891; G. Klemperer, *Deutsch. med. Wochenschr.*, No. 15: 1891.

[2] Fürbringer, *Virchow's Arch.*, vol. lxiii. p. 39: 1878.

[3] Liebermeister, *Deutsch. Arch. f. klin. Med.*, vol. vii. p. 75: 1870; and vol. viii. p. 153: 1871; "Handbuch d. Patholog. u. Therapie d. Fiebers," Leipzig: Vogel, 1875.

[4] Leyden, *Deutsch. Arch. f. klin. Med.*, vol. v. p. 237: 1869; and vol. vii. p. 536: 1870. *Centralbl. f. d. Med. Wissensch.*, No. 13: 1870.

[5] Silujanoff, *Virchow's Arch.*, vol. liii. p. 327: 1871; A. Fränkel, *Verhandl. d. physiolog. Gesellsch. z. Berlin*, 4th Feb. 1894; E. Leyden and A. Fränkel, *Centralbl. f. d. med. Wissensch.*, p. 706: 1878; *Virchow's Arch.*, vol. lxxvi. p. 136: 1879.

[6] Colasanti, *Pflüger's Arch.*, vol. xiv. p. 125: 1876; D. Finkler, *idem*, vol. xxix. p. 89: 1887; A. Lilienfeld, *idem*, vol. xxxii. pp. 293–356: 1883.

[7] Senator, *Virchow's Arch.*, vol. xlv. p. 351: 1869. "Unt. üb. d. fieberhaften Process u. seine Behandl.," Berlin, Hirschwald, 1873. *Du Bois' Arch.*, p. 1: 1872; Wertheim, *Deutsch. Arch. f. klin. Med.*, vol. xv. p. 173: 1875. *Wiener med. Wochenschr.*, Nos. 3–7, 1876; Nos. 32, 34 and 35, 1878. Fr. Kraus, *Zeitschr. f. klin. Med.*, vol. xviii. p. 160: 1891. A. Loewy, *Virchow's Arch.*, vol. cxxvi. p. 218: 1891.

[8] L. Traube, *Allgem. med. Centralzeitung*, July 1, July 8 and Dec. 22, 1863, and March 23, 1864. "Ges. Beiträge z. Patholog. u. Physiolog.," Berlin, Hirschwald, vol. ii. pp. 637 and 679: 1871. A list of the numerous authors who prior to Traube have put forward the theory of diminished heat loss in fever, although

in fever a constriction of the peripheral blood-vessels occurred with diminished flow of blood to the skin, so that there was diminished heat loss, accompanied by congestion in the interior of the body. By means of Mosso's plethysmograph, Maragliano showed that in various febrile diseases the cutaneous vessels contracted, and moreover that they commenced doing so before the rise of temperature was perceptible. As contraction continued, the temperature began to rise, both reaching the maximum at the same time. An expansion of the blood-vessels preceded the fall in temperature, which came down to normal while the blood-vessels were still maximally dilated.[1]

The diminished loss of heat, especially in the first stages of fever, has, with the help of the calorimeter, been proved by many observers from direct experiments on man and animals.[2]

Many unsuccessful attempts have been made to decide experimentally what part the nervous system takes in the increased metabolism and the diminished loss of heat. Numerous experiments on animals have shown that by mechanical injury or electrical stimulation of certain parts of the brain — *e. g.*, the median portion of the corpus striatum, &c., a lasting rise of temperature may be induced, accompanied by increased metabolism. But this is a different process from that involved in fever, since there is neither contraction of the blood-vessels nor diminished loss of heat.[3]

Of the two factors which bring about a rise of temperature in fever, *i. e.*, the increased production of heat by more rapid metabolism and the diminished loss of heat, the latter is certainly the more important, since, as I have already mentioned, a febrile condition may occur in the absence of the first factor. Some authors indeed have gone so far as to regard the first factor, increased metabolism, as the consequence and

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perhaps not in so clear and decisive a manner, will be found in Maragliano, *Zeitschr. f. klin. Med.*, vol. xiv. p. 309: 1888, where a careful notice of the literature on the subject is also given.

[1] Maragliano, *loc. cit.*, pp. 316–319.

[2] Senator, "Unt üb. d. fieberhaften Process u. seine Behandlung." Berlin, Hirschwald, 1873. Carl Rosenthal, *Du Bois' Arch.*, p. 1: 1888. J. Rosenthal, *Berlin. klin. Wochenschr.*, p. 785: 1891, and "Internat. Beiträge z. wissenschaftl. Med.," Festschrit., R. Virchow gewidmet. Berlin, Hirschwald, vol. i. p. 413: 1891.

[3] Further discussion of these experiments would be beyond the scope of this text-book. For further references I will mention: J. Ott, *Journ. of Nervous and Mental Diseases*, 1884, and *Therapeutic Gazette*, Sept. 15, 1887; *The Medical News*, Dec. 10, 1887; Aronsohn and Sachs, *Pflüger's Arch.*, vol. xxxvii. p. 232: 1885; H. Girard, *Arch. de Physiol.*, Série III. vol. viii. p. 281: 1886: and Série IV., vol. i. pp. 312, 463: 1888; Hale White, *Journ. Physiol.*, vol. ii. Nos. 1 and 2 1890; Ugolino Mosso, *Arch. f. exper. Path. u. Pharmakol.*, vol. xxvi. p. 316: 1890.

not as the cause of the rise in temperature, since direct experiments on animals and on man have shown that, if the temperature be artificially raised and the loss of heat be at the same time prevented by warm baths, the excretion of urea is increased.[1]

It is however very doubtful whether this increase in urea observed with an artificial rise of temperature is a sufficient explanation of the large quantity of additional urea eliminated in fever. The increase of urea brought about by artificial means was always much less than that in fever, and, in fact, in some experiments it did not occur at all.[2] Moreover the theory that increased metabolism is due to the rise of temperature is belied by the fact that the increased nitrogenous excretion in fever does not run parallel with the heightened temperature, but usually reaches its maximum after the crisis.[3] In many cases the rise of temperature is only slight during the febrile stage, and yet there is a large increase in the urea excretion after the fever has abated. In one case of recurrent fever 47.8 g. of urea were excreted on the second day after the crisis,[4] in a case of typhus exanthematicus 160 g. of urea on the third and fourth days after the temperature had fallen.[5] Occasionally in diseases due to infection the proteid disintegation may even precede the rise of temperature.[6] Schimanski[7] showed that, if pus was injected into fowls, there was frequently no alteration in temperature, although a large additional amount of nitrogen was excreted. Lilienfeld[8] found that after pyogenic injections an increase in the intake of oxygen and output of carbonic acid occurred, even when the rise of temperature was prevented by cold baths.

From these experiments we see that the increase in metabolism is not a consequence of the rise of temperature. On the other hand, it is not improbable that the increased metabolism—especially in the later stages of the febrile process—may

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[1] Bartels, *Griefswalder med. Beitr.*, vol. iii. p. 36: 1865; Naunyn, *Berl. klin. Wochenschr.*, p. 42 : 1869; *Du Bois' Arch.*, p. 159 : 1870 ; Schleich, *Arch. f. exper. Path. u. Pharm.*, vol. iv. p. 82 : 1875 ; P. Richter, *Virchow's Arch.*, vol. cxxiii. p. 118: 1891; R. Topp, *Therapeut. Monatshefte*, pp. 1, 55: 1894.

[2] C. F. A. Koch, *Zeitschr. f. Biol.*, vol. xix. p. 447 : 1883 ; N. P. Simanowsky, *Zeitschr. f. Biol.*, vol. xxi. p. 1 : 1885.

[3] Anderson, *Edinb. Med. Journ.*, p. 708: Feb. 1866. Compare Wood and Marshall, *Journ. of Nerv. and Ment. Diseases*, No. 1 : 1891.

[4] A. Pribram and J. Robitschek, *Prag Vierteljahrsschr.*, vol. civ. p. 318: 1869.

[5] Naunyn, *Arch. f. exper. Path. u. Pharm.*, vol. xviii. p. 83 : 1884.

[6] Sydney Ringer, *Lancet*, Aug. 6, 1859.

[7] Schimanski, *Zeitschr. f. physiol. Chem.*, vol. iii. p. 396 : 1879.

[8] A. Lilienfeld, *Pflüger's Arch.*, vol. xxxii. p. 293 : 1883.

be partly referred to the death of the affected tissues, which must be got rid of when they have undergone disintegration. This death of individual tissue-elements may be traced by direct anatomical observation.[1]

The red blood-corpuscles are among the elements which are destroyed in this way, as evidenced by the production of a larger amount of urobilin.[2] (Compare pp. 323, 339.) The leucocytes, on the other hand, are usually augmented in most of the zymotic diseases, as in the case of many other disturbances, which are connected with increased disintegration of the tissues. It appears that the object of the multiplication of the leucocytes is to render the waste-products harmless. Direct experiments have shown that the number of leucocytes rises on the introduction of foreign substances of the most varied nature into the body.[3]

There is probably a connection between the increased disintegration of proteid and the occurrence of organic acids — volatile fatty acids[4] and lactic acid[5] — as well as the diminution of the alkalescence of and the carbonic acid in the blood, and the passage of aceton, aceto-acetic acid, oxybutyric acid,[6] and volatile fatty acids[7] into the urine. (Compare pp. 391, 392.) The amount of carbonic acid in the arterial blood may sink to 10.7 vol. per cent.[8] The increased elimination of ammonia in fever (which may rise to as much as 2.7 g. per diem[9]) may be connected with the increased formation of these organic acids. (Compare pp. 292, 404.) The appearance of acids in the blood, the diminution of the alkalescence and of the carbonic acid have been likewise observed as results of the action of inorganic

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[1] These experiments are described by Liebermeister, "Handb. d. Patholog. u. Therap. d. Fiebers.," chap. iv. p. 437, Leipzig, Vogel: 1875.

[2] G. Hoppe-Seyler, *Virchow's Arch.*, vol. cxxiv. p. 30: 1891; and vol. cxxviii. p. 43: 1892. In the former volume all the previous work on the occurrence of urobilin in disease is collected.

[3] An account of the complete and comprehensive literature on the behavior of the leucocytes is given in the monograph of H. Rieder, "Beitr. z. Kenntniss d. Leukocytose," Leipzig, Vogel: 1892. Compare also Lecture XV. p. 222.

[4] von Jaksch, "Klinische Diagnostik," 2d edition, p. 59: 1889.

[5] Minkowski, *Arch. f. exper. Path. u. Pharm.*, vol. xix. p. 209: 1885.

[6] Deichmüller, *Centralbl. f. klin. Med.*, No. 1: 1882. Seifert, *Verhandl. d. Würzburger phys.-med. Ges.*, vol. xvii. p. 93: 1883. Litten, *Zeitschr. f. klin. Med.*, vol. vii. Suppl. p. 82: 1884. Penzoldt, *Deutsch. Arch. f. klin. Med.*, vol. xxxiv. p. 127: 1884. v. Jaksch, "Ueb. Acetonurie u. Diacetonurie," Berlin: 1885. Külz, *Zeitschr. f. Biolog.*, vol. xxiii. p. 336: 1887.

[7] von Jaksch, *Zeitschr. f. physiol. Chem.*, vol. x. p. 536: 1886.

[8] Jul. Geppert, *Zeitschr. f. klin. Med.*, vol. ii. p. 355: 1881. Compare also Minkowski, *loc. cit.*

[9] Hallervorden, *Arch. f. exper. Path. u. Pharm.*, vol. xii. p. 249: 1880. This author also quotes the earlier work of Duchek and Koppe. Compare also Bohland, *Pflüger's Arch.*, vol. xliii. p. 30: 1888; and G. Gumlich, *Zeitschr. f. physiol. Chem.*, vol. xvii. p. 30: 1892.

poisons, such as arsenic, phosphorus, &c.;[1] and it appears therefore as if the toxins, which are the metabolic products of the pathogenic bacteria and which occasion the febrile zymotic diseases, involve a similar disturbance in the chemistry of the blood.

Albuminuria,[2] although not an invariable, is yet a frequent accompaniment of high fever. Its connection with the other changes in the chemistry of fever is not yet explained. It would be an obvious assumption that the kidneys, in endeavoring to rid the organism of the infective substances or even of the pathogenic microörganisms themselves, become irritated by these poisons which thus produce albuminuria. It has in fact been stated that poisonous substances are to be found in the urine of febrile patients.[3] Brieger and Wassermann,[4] in examining the urine of a case of erysipelas, succeeded in isolating a toxalbumin which had a poisonous effect on guinea-pigs. The disease in which the pathogenic bacilli themselves have, so far, been found in the kidneys are pyemia, anthrax, glanders, diphtheria, scarlet fever, erysipelas, pneumonia, typhoid, and recurrent fever.[5] In typhoid, the specific bacteria were found by Konjajeff[6] occasionally in the urine, as well as in the kidneys. In eleven out of forty-eight cases of the same malady, Neumann[7] detected bacilli in the urine. Karlinski[8] asserts that the typhoid bacilli can be detected far more readily in the urine than in the feces. Whereas in the latter they could not be discovered until the ninth day of the disease, they were frequently found in the urine as early as the third day. Bacilli were found in twenty-one out of forty-four cases.

There is another change which often occurs in the metabolism in febrile diseases, *i. e.*, the diminution, often very remarkable, in the excretion of chlorin. This substance sometimes almost

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[1] Hans Meyer and Fr. Williams, *Arch. f. exper. Path. u. Pharm.*, vol. xiii. p. 70: 1881. Hans Meyer, *idem*, vol. xiv. p. 313: 1882; and vol. xvii. p. 304: 1883.

[2] The literature is given by Senator, "Die Albuminurie," 2d edition, Berlin, Hirschwald: 1890. Compare also Hübener, "Ueb. Albuminurie b. Infectionskrankheiten," Diss., Berlin: 1892.

[3] The following works may be selected from the voluminous literature: Bouchard, "Leçons sur les auto-intoxications," Paris: 1887. F. Selmi, *Accad. d. scienze di Bologna*, 1879; and *Ann. di chim. e. di farm.*, vol. viii. p. 3: 1888. Compare also the discordant results of E. Bonardi, *Riv. clinica*, p. 389: 1890.

[4] Brieger and Wassermann, *Charité-Annalen*, Jahrg. 17, p. 834: 1892.

[5] Ribbert, *Deutsch. med. Wochenschr.*, No. 39, p. 805: 1889. This author quotes the literature on this subject.

[6] Konjajeff, *Jescheniedielnaja klinitscheskaja Gazeta*, Nos. 33–38: 1888. Summarized in *Centralbl. f. Bacteriolog. u. Parasitenkunde*, vol. vi. p. 672: 1889.

[7] H. Neumann, *Berlin. klin. Wochenschr.*, No. 6: 1890.

[8] J. Karlinski, *Prag. med. Wochenschr.*, Nos. 35 and 36: 1890.

entirely disappears from the urine in cases of croupous pneumonia.[1] This symptom is however merely temporary, and does not last more than three days at the most.[2] No one has yet succeeded in explaining this phenomenon or of determining its connection with the other symptoms of fever.

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[1] J. F. Heller, *Heller's Arch. f. physiol. u. patholog. Chem. u. Mikroskop.* vol. iv. p. 523: 1847; Redtenbacher, *Zeitschr. d. Ges. d. Aerzte in Wien.*, p. 373: 1850; S. Moos, *Zeitschr. f. rat. Med.*, N. F., vol. vii. p. 291: 1855; E. Unruh, *Virchow's Arch.*, vol. xlviii. p. 227: 1869; Röhmann, *Zeitschr. f. klin. Med.*, vol. i. p. 513: 1880; R. Klees ("Over chloorvermindering in de urine," &c., Diss., Amsterdam: 1885) attempts to show that the diminished excretion of chlorin in acute diseases is connected with a disturbance in the renal function (albuminuria).

[2] C. G. Lehmann, *Lehr. d. physiol. Chem.*, vol. ii. p. 392, Leipzig: 1850.

LECTURE XXIX

THE DUCTLESS GLANDS: THE SUPRARENAL CAPSULES, THE THYROID GLAND, THE PITUITARY BODY

THERE are three organs in our body which have the epithelial structure of glands, but are without ducts: the suprarenal capsules, the thyroid gland, and the pituitary body. If we would attribute to these organs functions similar to those of the glands, we must assume that they obtain from the blood certain substances which undergo alteration in their epithelial cells, the products of conversion being again returned to the blood. These changes must be of the greatest importance in the vital process, since extirpation of the suprarenal capsules as well as of the thyroid gland is followed by the death of the animal upon which the experiment is made.

In consequence of the well-known discovery, published in 1855 by Addison,[1] concerning the relation of bronzing of the skin to disease of the SUPRARENAL CAPSULES, Brown-Séquard[2] investigated the results of the extirpation of these organs in animals. He showed that such animals as rabbits, guinea-pigs, cats, dogs and mice never survived the excision of both suprarenals for more than two days at the most. After the removal of only one suprarenal they lived for a longer time, and Brown-Séquard considered that they might possibly be kept permanently alive. This author endeavored by numerous experiments to prove that death after excision of both suprarenal capsules was not brought about by the operative interference—the animals survived extirpation of the kidneys longer than they did that of the organs under discussion—nor by the injury done to the numberless nerve-fibers which run from the suprarenals to the plexus semilunaris, but to the abolition of the suprarenal functions. He showed that if the blood of an animal, which was dying in consequence of the removal of its suprarenal capsules, were injected into a vein

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[1] Thos. Addison, "On the constitutional and local effects of disease of the suprarenal capsules": London, 1855.

[2] E. Brown-Séquard, *Comptes rendus*, vol. xliii. pp. 422 and 542: 1856; and vol. xiv. p. 1036: 1857.

of another animal in whom only one of these organs had been cut out, the death of the second animal was hastened. Again, if the blood of a normal animal were injected into a vein of an animal, which was dying from the effects of excision of both suprarenals, the life of the latter was prolonged.

Brown-Séquard is therefore the founder of the modern doctrine concerning the functions of the ductless glands, *i. e.*, that these glands convert injurious into harmless substances and produce the substances which are necessary for the normal functioning of other organs. This work of the ductless glands is termed "internal secretion." We may however here remark that, besides the preparation of the secretions which are discharged by the ducts, the glands properly so called may also be forming an important internal secretion, as already proven in the cases of the pancreas (p. 400) and liver (p. 334).

These operations of Brown-Séquard have been more recently repeated with aseptic precautions, and the results confirmed.[1] The animals experimented upon never survived extirpation of both suprarenals for more than a few days. A different result was however obtained by J. Pal,[2] who succeeded in keeping a dog alive for 4½ months after excision of both suprarenals. Pal controlled his experiments by an autopsy, thus removing the obvious objection that the excision might have been incomplete. We must also take note of the statement that rats are not affected by excision of the suprarenals.[3] In one of the latest researches on the subject by Szymonowicz[4] however this author declares his conviction that dogs never survive the extirpation of both capsules for more than fifteen hours at the most, and that the statements of previous experimenters to the contrary were either due to incomplete excision or to the fact that accessory suprarenals were left behind.

Investigation of the functions of the suprarenal capsules is rendered peculiarly difficult owing to the fact that this organ is rich in sympathetic ganglion cells, from which numerous fibers pass to other parts of the sympathetic nervous system. For this reason operations on the suprarenals cause indirect disturbances of the most varied nature.[5]

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[1] F. and S. Marino-Zucco, *Atti della R. Accad. dei Lincei*, S. V., vol. i. p. 122: 1894; *Riforma med.*, vol. i. p. 709: 1894; E. Abelous and P. Langlois, *Comptes rend. Soc. biol.*, vol. xliv. pp. 165, 388, 410, 490, 864: 1892. L. Szymonowicz, *Pflüger's Arch.*, vol. lxiv. p. 97: 1896.

[2] J. Pal, *Wien. klin. Wochenschr.*, p. 899: 1894.

[3] E. Boinet, *Comp. rend. Soc. biol.*, vol. xlvii. pp. 273, 325, 498: 1895.

[4] L. Szymonowicz, *Pflüger's Arch.*, vol. lxiv. p. 97: 1896.

[5] G. Tizzoni, *Arch. ital. de Biolog.*, vol. vii. p. 372: 1888. G. Jacoby, *Arch. f. exper. Path. u. Pharm.*, vol. xxix. p. 171: 1891. N. de Dominicis, *Arch. de Physiol.*, vol. xxvi. p. 810: 1895. J. Pal, *loc. cit.*

A voluminous literature has of recent years appeared on the specific constituents of the capsules, on the poisons which are stored up in them,[1] on the substances, which the suprarenals pass on to the blood and which are supposed to have an influence on the innervation of the blood-vessels, heart, and respiratory organs,[2] on the chromogens in the capsules, which are considered to be related to the dark pigment that is deposited in the skin in Addison's disease,[3] etc. But for the present it is not possible to give a short connected account of the indefinite and contradictory statements.

An interesting observation has been made on animals, from whom only one capsule had been removed, viz., that black patches appeared on the skin,[4] corresponding to the dark pigmentation in patients suffering from Addison's disease.

The discovery that the THYROID GLAND was, like the suprarenals, indispensable to the animal economy, was again made in the domains of pathology. The earlier experiments and speculations of the physiologists concerning the significance of the thyroid gland had not borne any fruit.

In 1873 Sir William Gull[5] showed at the Clinical Society in London five cases of a disease to which he was the first to call attention, and which he termed "a cretinoid state supervening in adult life in women." In 1878 William M. Ord[6] described five other cases of the same malady. An invariable symptom is present in the thickening and swelling of the skin, which occurs usually in the face but sometimes extends also to the extremities and other portions of the body, as well as to the mucous membranes of the internal organs. This thickening cannot be regarded as edema; if the swollen skin be cut, no serum flows out. It is due to an active new formation of a connective tissue rich in mucin. On account of the invariable occurrence of this symptom Ord called the disease "myxedema." Other trophic disturbances were likewise present: dryness of the skin in consequence of insufficient secretion of sweat and sebum, baldness, atrophy of the nails and teeth, etc. By

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[1] P. Foa e P. Pellacani, *Arch. p. l. scienze med.*, vol. vii. p. 113: 1883. S. Fränkel, *Wien. med. Blätter*, Nos. 14, 15 and 16: 1896.

[2] G. Oliver and E. A. Schäfer, *Proc. Physiol. Soc.*, March 10, 1894, and March 16, 1895, L. Szymonowicz, *loc. cit.*

[3] Vulpian, *Comptes rend.*, vol. xliii. p. 663: 1856. M'Munn, *Journ. Physiol.*, vol. v. p. 24: 1885. Krukenberg, *Virchow's Arch.*, vol. ci. p. 542: 1885. S. Fränkel, *Wien. med. Blätter*, Nos. 14, 15, 16: 1896. *Wien. klin. Wochenschr.*, p. 212: 1896. G. Caussade, *Comptes rend. Soc. biol.*, p. 67: 1896. O. v. Fürth, *Zeitschr. f. physiol. Chem.*, vol. xxiv. p. 1: 1897.

[4] F. and S. Marino-Zucco, *loc. cit.*

[5] Wm. Gull, *Trans. Clin. Soc.*, Lond.: 1874.

[6] William M. Ord, "On Myxedema," *Medico-chirurg. Trans.*, 2d ser., vol. xliii. p. 57: 1878.

degrees physical and mental feebleness supervenes, which in many respects resembles cretinism.

Ord had already observed a shrinking of the thyroid gland and the destruction of its follicle through the swelling connective tissue,[1] but he looked upon it merely as a consequence of the general myxomatous new-formation in the connective tissue. He did not yet recognize that the degeneration of the thyroid gland was the primary factor in the disease. Ord called attention to the analogy between myxedema and cretinism, and emphasized the fact that the latter condition is frequently associated with the colloid degeneration of the thyroid gland known as goiter.[2] But he did not regard the change in the gland as being the cause of cretinism. The connection between the degeneration of the thyroid gland and the symptoms of myxedema and cretinism was first recognized by the Swiss surgeons Reverdin and Kocher.

On 13th September 1882 J. L. Reverdin[3] described before the Medical Society of Geneva the effects of fourteen complete extirpations of goiters, and in April 1883 the two Genevese surgeons J. L. Reverdin and A. Reverdin published in detail the results of removing goiters in twenty-two cases.[4] Of these fourteen were complete, *i. e.*, excision of the whole diseased and of the remaining sound tissue of the thyroid gland. As a consequence of complete removal, they observed symptoms which bore a striking resemblance to those of myxedema and of cretinism, *i. e.*, swelling of the skin of the face and extremities, diminished perspiration, slowness and heaviness in the movements as well as in the psychical functions,[5] besides anemia, a readiness to fatigue, a sensation of cold, and occasionally tetany.

The extirpation of the thyroid gland thus led to a series of symptoms which resembled myxedema, in which disease the thyroid gland undergoes degeneration.[6] We may therefore conclude that it is the absence of the function of the thyroid gland which causes the symptoms in both cases, viz.—the extirpation and degeneration of the gland.

At the same time as Reverdin,[7] Kocher was likewise

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[1] Ord, *loc. cit.*, pp. 60, 67, 72, 73. B. Hadden, *Brain*, p. 193: 1883, and Hun and Prudden, *The American Journ. of the Med. Sciences*, vol. xcvi.: 1888.

[2] Ord, *loc. cit.* p. 73. He here quotes the earlier authors who discuss the question as to the connection between cretinism and goiter.

[3] J. L. Reverdin, *Revue méd. d. l. Suisse romande*, 2 ieme Ann., p. 539: 1882.

[4] *Revue méd. d. l. Suisse romande*, 3ieme Ann., pp. 169, 233, and 309: 1883.

[5] Reverdin, *loc. cit.*, pp. 352 and 355.

[6] *Idem*, *loc. cit.*, p. 356.

[7] In his first communication (*Revue méd. d. l. Suisse romande*, p. 540: 1882) Reverdin mentions a previous communication of Kocher's on the consequences of total excision of goiter.

engaged at Berne in performing the same operation of complete extirpation; and in April 1883 he communicated the results of his abundant experience at the Congress of the German Surgical Society.[1] These symptoms which occurred after total excision were in all respects identical with those described by Reverdin. If however a minute portion of the gland were left, so that a small fresh growth of thyroid took place,[2] these symptoms did not occur. To the latter, Kocher gives the name of cachexia strumipriva,[3] and he describes them as follows[4]:

Soon after their dismissal from the hospital, or in a few cases, not until four or five months afterwards, the patients begin to complain of lassitude, weakness, and weight in the limbs. This is soon followed by a sensation of cold. In the winter time the hands and feet become cold, swollen, of a purple color, and chilblains ensue. The mental condition is impaired; thought and speech become slower. All movements get slower and more languid. At the same time swellings appear on the face, hands, and feet; in a few cases these are at first temporary, and subsequently they become permanent. The thickness of the face and the heaviness of the movements give the appearance of idiocy. The whole skin seems swollen and can only be raised from the body in large folds. Its surface is dry, with scurf on the ears and cheeks, and the hair falls out. In advanced cases, anemia is present to a marked degree. The number of red blood-corpuscles was usually under 4 millions per cb. mm., in four cases it sank to lower than 2.8 millions, and in one case even to 2.2 millions. The white blood-corpuscles were relatively somewhat increased. The anemia developed gradually, and grew progressively worse as time elapsed after the operation. If at the time of the operation the patients were children who were growing fast, the stature was at once arrested in a striking manner. In many cases attacks of vertigo were observed, but convulsions were only noted in one instance, that of a girl. The excellent development of the muscles formed a curious contrast to the patients' complaints of feebleness and lassitude.

The numerous excisions of goiters which have been carried out in Billroth's hospital practice in Vienna have led to divergent results, in so far as the cases were much more frequently complicated with tetany than they were at Berne.

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[1] Kocher, *Arch. f. klin. Chirurgie*, vol. xxix. p. 254: 1883.

[2] *Idem, loc. cit.*, p. 278.

[3] *Idem, loc. cit.*, p. 285.

[4] *Idem, loc. cit.*, p. 279, *et seq.*

A. v. Eiselsberg,[1] who has collected the statistics of fifty-three complete excisions performed in Billroth's clinique, states that attacks of tetany occurred in twelve cases, eight of which died in consequence. It is noteworthy that all the twelve patients were females.

Kocher considers that the arrest of physical and mental development in cretinism is also due to disease of the thyroid gland.[2] It is true that all cretins do not have goiters ; according to the statistics of a French Commission the proportion is somewhat more than 75 per cent. But it must not be overlooked that in most cases cretinous children are descended from goitrous parents, and that cretinism is inherited through several generations.[3]

From these pathological facts, a number of physiological questions arise. We see that the failure of the thyroid function is the signal for the onset of the gravest physical and mental disturbances. What is the connection between these functions? Are the substances which act harmfully upon the organism altered and rendered innocuous as they pass through the gland? Or are substances formed in this organ which are essential to the performance of physical and mental functions? Or may both these phenomena occur? The fact already mentioned that a small remnant of the thyroid gland is able to take the place of the whole appears to show that the active principle of the organ need only be present in a minute quantity in order to affect the total metabolism, that in fact it is a question of so-called ferment-action. Physiological experiment on animals seems to confirm this view.

In 1884 Schiff[4] published an account of his experiments on the extirpation of the thyroid gland in dogs, adding that he had already written about them in 1859 but that no notice had been taken of them by the surgical profession. Schiff found that after complete extirpation of the thyroid gland all the animals died from four to twenty-seven days afterwards. These experiments have been confirmed by many observers. The symptoms shown by the animals subsequent to the operation were however of very variable character, not only in

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[1] A. von Eiselsberg, "Ueber Tetanie im Anschluss an Kropfoperationen," Wien, A. Hölder: 1890. This author also gives a complete account of the literature on the consequences of excision of goiters.

[2] Kochner, *loc. cit.*, p. 298 *et seq.*

[3] The copious literature on the connection between goiters and cretinism is quoted by A. Hirsch, "Handb. d. historisch-geographischen Patholog.," 2d edition, Part II. pp. 137–140 : 1883.

[4] M. Schiff, *Rev. méd. d. l. Suisse rom.*, Ann. iv. p. 65, 15 Fév. : 1884. Transl. in *Arch. f. exper. Path. u. Pharm.*, vol. xviii. p. 25 : 1884.

different species, but also in different individuals of the same species. A few of the animals succumbed rapidly in a few days, frequently with the accompaniment of tetany; others lived for some months or even longer, and sank gradually from general cachexia. The causes of this divergent behavior have not so far been explained in any way, and the accounts are very discordant.[1]

Horsley[2] found that older animals survived excision of the thyroid for a longer time than young animals, and recalls the observation of the anatomist Huschke that this organ is relatively larger in youth, and diminishes with age. The thyroid would thus appear to take a prominent part in the development of the tissues. Moussu,[3] Hofmeister,[4] and others obtained the same results as Horsley.

In dogs and cats thyroidectomy is usually fatal. The first symptoms are those of general weakness, twitchings of the muscles, and disturbance of the regulation of the temperature. The muscular twitchings first appear as fibrillar, and subsequently as clonic and tonic convulsions, and in the worst form are of an epileptic character, followed by Cheyne-Stokes respiration and deep coma. That this muscular excitation is of central nervous origin was first shown by Schiff,[5] who pointed out that the muscular tremors and the convulsions were abolished by cutting through the peripheral nerves. If in dogs the spinal cord be divided at the level of the eighth dorsal vertebra, the characteristic convulsions which occur on excision of the thyroid gland are confined to the fore limbs.[6] In a few cases feeble isolated twitches were also observed in the hinder extremities. The impulse for the spasmodic movements of the extremities evidently travels from the brain to the spinal cord by way of the pyramidal tracts. That the disturbances consequent upon thyroidectomy are mainly of central origin agrees well with the observations on man: *e. g.*, the slowness of thought and speech ending ultimately in loss of mental power. In the case of dogs, death generally occurs

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[1] On this question see V. Horsley, "Internat. Beitr. z. wissensch. Med.," Festschr., R. Virchow gewidmet., vol. i. p. 382 *et seq.*: 1891. Over 200 publications are here critically discussed. See further A. von Eiselsberg, "Ueber Tetanie im Anschluss an Kropfoperationen," Wien, A. Hölder, p. 16: 1890.

[2] Victor Horsley, *Proc. Roy. Soc.*, vol. xl. p. 7: 1886.

[3] G. Moussu, *Mém. Soc. Biol.*, p. 271: 1892.

[4] Hofmeister, *Beitr. z. klin. Chirurg.*, vol. xi.: 1894.

[5] M. Schiff, *Rev. méd. d. l. Suisse rom.*, Ann. iv. p. 71: 1884. Compare O. Lanz, *Mitth. a. Kliniken u. med. Instituten d. Schweiz.*, vol. iii. p. 512: 1895; and Fr. de Quervain, *Virchow's Arch.*, vol. cxxxiii. p. 481: 1893.

[6] O. Lanz, *Mitth. a. Kliniken u. med. Instituten d. Schweiz.*, vol. iii. p. 516: 1895.

within the first fortnight during an attack of tetany.[1] Occasionally however, a dog will survive the operation.[2]

In the case of rabbits the accounts are so much at variance that for the present no reliable deductions can be drawn.[3] E. Gley[4] found that excision of the thyroid in rabbits was not followed by death unless the small accessory thyroids[5] were removed at the same time, and that in these cases the animals generally succumbed with signs of tetany. F. Hofmeister[6] found that after the extirpation of the thyroid in young rabbits cachexia was the invariable result, tetany occurring if the accessory glands were likewise removed. Other effects observed by him were retardation of the growth of bone and the ossification of the epiphyses. Blumenreich and Jacoby[7] contest Gley's assertion. They found that it made no difference whether the accessory glands were removed with the thyroid body or not. The behavior of the rabbits on whom thyroidectomy has been performed varied greatly in every particular. Many became cachectic, but tetany seldom occurred. Some died soon after the operation, others did not succumb until months later of some intercurrent disorder. In the animals suffering from cachexia, atrophy of the lymphoid tissues, and especially of the thymus, was observed, besides disturbances of the biliary secretion and marked distention and enlargement of the gastric intestinal canal. Lanz[8] states that all the rabbits in which he excised the gland died either of acute or of chronic tetany.

In the case of sheep, goats, and donkeys, cachexia did not supervene until long after the operation.[9] In young goats and lambs v. Eiselsberg[10] noticed that the growth of the bone-substance was arrested both in length and breadth, and that

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[1] P. M. Autokratow, *Petersburg. Wochenschr.*, p. 105 : 1888: G. Fano e. L. Janda, *Archivio medico*, vol. xiii. p. 365 : 1889; O. Lanz, *loc. cit.* p. 512 : 1895.

[2] Ed. Wormser, *Pflüger's Arch.*, vol. lxvii. pp. 533–536 : 1897. Compare Drobnik, *Arch. f. exper. Path. u. Pharm.*, vol. xxv. p. 136 : 1888; and R. Schwarz, *Lo Sperimentale*, Fasc. 1 : 1892.

[3] *Vide* F. Mertens, Zur Kenntniss d. Schilddrüse," Diss., Göttingen : 1890; J. R. Ewald u. John Rockwell, *Biol. Centralbl.*, p. 568 : 1890.

[4] E. Gley, *Arch. de Physiol.*, Jan. and Apr. 1892, p. 467 : 1893; p. 101 : 1894; p. 136 : 1897; and *Pflüger's Arch.*, vol. lxvi. p. 308 : 1897. The literature of the subject will be found quoted here.

[5] For the construction of the accessory thyroid glands see H. Cristiani, *Arch. de Physiol.*, p. 279 : 1893.

[6] F. Hofmeister, *Beitr. z. klin. Chir.*, vol. xi.: 1894.

[7] L. Blumenreich and M. Jacoby, *Berl. klin. Wochenschr.*, p. 327 : 1896; and *Pflüger's Arch.*, vol. lxiv. p. 1 : 1896.

[8] O. Lanz, *Mitth. a. Kliniken d. Schweiz.*, vol. iii. p. 541 : 1895.

[9] V. Horsley, *Internat. Beitr. z. wissenschaftl. Med.*, vol. i. pp. 390 and 391; 1891.

[10] A. v. Eiselsberg, *Langenb. Arch. f. klin. Chir.*, vol. xlix. p. 207 : 1895.

development of the horns and hair was affected; these symptoms were accompanied by a fall in temperature and general apathy, recalling cretinism in man. Tetany however did not occur either in these cases nor in the case of the herbivora upon which Lanz[1] had performed thyroidectomy. Philipeaux[2] states that removal of the thyroid gland had no effect upon white rats, but it may be doubted whether these investigations were pursued far enough. Cristiani[3] showed that rats, as well as domestic and field mice, have accessory thyroids, excision of which, together with the main gland, produces death from tetany.

The consequences incident on the extirpation of the thyroid glands in monkeys are described by Victor Horsley as follows[4]:

Fibrillar muscular twitchings of the extremities may result immediately; but as a rule the animal remains quite healthy for the first five days. These twitchings develop in twenty-four hours into tetanic attacks, which usually last for about twenty days and then gradually cease. At the same time the symptoms of myxedema and cretinism slowly develop; the animal becomes more and more apathetic, taking no notice of anything, in marked contrast to its former vivacity. The skin on the face and abdomen becomes swollen. According to the analysis made by Halliburton this swelling is due to infiltration with mucin. The salivary glands are markedly hypertrophied, and the parotid, which normally yields a liquid secretion, now produces a thick saliva containing an abundance of mucin. The blood shows extensive changes; the red blood-corpuscles diminish, the white ones are at first increased and subsequently likewise diminish; the blood now contains mucin and the serum albumin is lessened. The body-temperature, which had risen somewhat after the operation, becomes variable, and gradually falls after about twenty-five days far below normal. The animal dies in a state of coma.

In a second communication[5] Horsley states that he was able considerably to prolong the life of his monkeys if he obviated the consequences of this fall in their temperature. He kept the animals in a place maintained at a temperature of 32° C., and as soon as nervous symptoms, trembling of the muscles, &c., supervened, he put them in a hot-air bath of

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[1] O. Lanz, *loc. cit.*, pp. 513 and 543.

[2] Philipeaux, *Compt. rend. Soc. d. Biol.*, p. 606: 1884.

[3] H. Cristiani, *Arch. de Physiol.*, p. 39: 1893.

[4] V. Horsley, *Proc. Roy. Soc.*, vol. xxxviii. p. 6: 1885.

[5] V. Horsley, *loc. cit.*, vol. xl. pp. 7 and 8: 1896.

40.5° C. Under these conditions all the monkeys, with the exception of the very young animals, lived four to five times longer than the previous animals had done, that is to say, their duration of life, instead of only four to seven weeks, was now extended to as many months. The animals thus treated passed through three stages—a neurotic, myxedematous, and atrophic. The symptoms of the first stage were artificially combated and scarcely showed themselves. The myxedematous swellings were likewise diminished, and the parotid did not become enlarged. The final stage was marked by loss of flesh, functional paresis and paralysis, mental dulness, lowering of the blood-pressure and of the body-temperature, ending in death from coma.

On this subject we may describe two further observations made by other investigators. v. Eiselsberg[1] experimented on a young monkey (*Inuus ecaudatus*). A week after the extirpation an attack of tetany supervened, which recurred several times, and ended in complete apathy. Nine weeks after the operation the animal was found dead in the cage. Dissection showed that "the subcutaneous cellular tissue was remarkably pale, and in patches somewhat jelly-like."

Lanz[2] records the case of a monkey which after removal of its thyroid went into acute tetany, ending quickly in death.

Very few experiments in this connection have been made on birds. Ewald and Rockwell[3] found that pigeons survived the operation if it were performed with proper precautions. After the lapse of three months they did not notice any effects. Perhaps the effects were overlooked, and the birds may not have been sufficiently long under observation. Or must we assume that the thyroid in pigeons is in a rudimentary condition, and that other organs have taken over its functions?

The universal occurrence of the thyroid gland among all the vertebrata shows that it is of vital importance to the organism. It is found in all classes of fish, even in the lowest, the petromyzon; moreover, in the amphioxus and in the tunicata — the invertebrata which are most nearly allied to the vertebrata — it occurs as an extension of the front portion of intestine in a form analogous to its embryonic position in the higher animals.

Cristiani[4] cut out the thyroid gland in lizards and snakes,

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[1] A. von Eiselsberg, *Langenb. Arch. f. klin. Chir.*, vol. xlix. pp. 223–226: 1895.

[2] O. Lanz, *Mitth. a. Klinik. d. Schweiz.*, vol. iii. p. 513: 1895.

[3] J. R. Ewald and J. Rockwell, *Arch. f. d. ges. Physiol.*, vol. xlvii. p. 160: 1890. Compare O. Lanz, *infra*, p. 486.

[4] Cristiani, *Arch. de Physiol.*, vol. vii. p. 356: 1895; and *Rev. méd. de la Suisse rom.*, p. 37: 1895.

which invariably died after a longer or shorter time. Lanz[1] performed the same operation on skate at the experimental station at Naples. Although he could detect no characteristic symptoms of ill-health, yet they did not live so long as the normal Selachians, which were kept in the aquarium under the same conditions.

The observation that thyroidectomy is usually attended with less ill-effects in herbivora than in carnivora[2] led to the assumption that a meat diet was especially bad for animals which had been deprived of these glands. It was thought that dogs and cats bore the loss better on a milk diet.[3] On this account a chiefly vegetable diet has been recommended for persons suffering from cachexia strumipriva. Ughetti[4] could not however confirm the statements as to the favorable influence of milk and vegetables on the symptoms resulting from removal of the thyroid.

All observers are unanimous on one point, viz., that the untoward results, including death, of extirpation of the thyroid, are absent if even a small portion of the gland be left behind in its normal position. It can be proved also that removal of the thyroid is without effect if a little bit of the gland be transplanted to some other part of the body. Experiments of this nature had already been carried out by M. Schiff,[5] who transplanted the thyroid of one dog into the abdominal cavity of another, and, after two or three weeks extirpated the thyroid gland of the second dog. The operation was successful in two cases, in both of which the animals remained alive and well. Schiff's transplantation experiment has been frequently confirmed, especially by A. von Eiselsberg.[6] This observer extirpated the thyroid in fifty cats, and found that in every case the operation was followed by tetany and death. In another cat he now excised only half the gland, which he transplanted into the abdominal wall between the peritoneum and the fascia. A month later he removed the other half of the gland. The animal lived for another two months, and appeared normal in every respect. At the end of this time, *i. e.*, three months after the transplantation, Eiselsberg cut out the transplanted bit of

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[1] O. Lanz, *Mitth. a. Kliniken u. med. Instituten d. Schweiz.*, vol. iii. p. 486: 1895.

[2] G. Moussu, *Mém. de la Soc. de Biol.*, p. 271: 1892; O. Lanz, *loc. cit.*, p. 513: 1895.

[3] Leo Breisacher, *Du Bois' Arch.*, p. 509: 1890. *Cf.* Moussu, *l. c.;* Fr. de Quervain, *Virchow's Arch.*, vol. cxxxiii. p. 504: 1893; and O. Lanz, *l. c.*, p. 530.

[4] Ughetti, *Riforma medica*, December 1892.

[5] M. Schiff, *Rev. méd. de la Suisse rom.*, Ann. 4, p. 425: 1884.

[6] A. Freiherr v. Eiselsberg, *Wien. klin. Wochenschr.*, Jahrg. v. p. 81: 1892.

gland, which he found well supplied with blood by two fairly large vessels, and under the microscope presented a normal appearance. The abdominal wound was carefully closed, but on the evening of the next day typical tetany developed, and the animal died on the third day after the operation. Eiselsberg carried out this experiment four times with success.

These experiments are in so far instructive as they show that the fatal results of removal of the thyroid are not dependent on interference with nerves or the general circulation, as was formerly maintained.[1] Moreover the fatal results could be prevented or at any rate postponed by giving the operated animals thyroid glands of the same or other species to eat, although a continuance of this treatment was not without ill-effects on the general metabolism. These were especially marked by an increase in the nitrogenous excretion — an increase which is also observed even in normal animals.[2] A series of careful experiments by Fr. Voit[3] on the normal dog showed that thyroid administration caused not only increased proteid destruction but also increased excretion of carbon dioxid, so that the body-weight may fall to half its previous amount.[4]

It is worth noting that, according to Lanz,[5] the subcutaneous injection of the juice of the thyroid gland in normal animals brings about atrophy of the thyroid.

All attempts to isolate the active principle of the thyroid gland have so far led to no satisfactory result. Great interest was excited by Baumann's discovery of iodin[6] in the thyroid and by his suggestion that the active principle of the gland was an iodin compound. Previous observations had already suggested the investigation of the thyroid for iodin. Kocher, who had been treating goiter by means of thyroid extract, had been struck with the resemblance of its effects to those

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[1] A full and critical account of the literature on this subject is given by V. Horsley, in the "Internat. Beiträgen z. wissenschaftl. Med., Festschr. R. Virchow gewidmit," vol. i. p. 372 *et seq.*: 1891.

[2] E. Roos, *Zeitschr. f. physiol. Chem.*, vol. xxi. p. 19: 1895. B. Schöndorff, *Pflüger's Arch.*, vol. lxiii. p. 423, and vol. lxvii. p. 395: 1897. Here the comprehensive literature on the influence of the thyroid gland on metabolism will be found.

[3] Fr. Voit, *Zeitschr. f. Biol.*, vol. xxxv. p. 116: 1897. Here a critical account of the earlier literature is given.

[4] K. Georgiewsky, *Centralbl. f. d. med. Wissensch.*, No. 27: 1895.

[5] O. Lanz, *Correspondenzbl. f. schweizer Aerzte*, Jahrg. xxv. p. 293: 1895.

[6] E. Baumann, *Zeitschr. f. physiol. Chem.*, vol. xxi. p. 319: 1895; vol. xxii. p. 1: 1887. *München. med. Wochenschr.*, No. 14 and 20: 1896. Baumann and E. Roos, *Zeitschr. f. physiol. Chem.*, vol. xxi. p. 481: 1896. E. Roos, *ibid.*, vol. xxii. p. 16: 1897; and "Ueb. Schilddrüsentherapie u. Jodothyrin," Freiburg and Leipzig, Mohr: 1897.

observed in the ordinary treatment with iodin. Moreover it had been suggested that the occurrence of goiter in certain mountain valleys might be ascribed to the absence of iodin in these places, though subsequent more exact experiments had shown this idea to be devoid of foundation, iodin being contained in the drinking-water as well as in the plants of certain valleys where goiter was endemic.[1]

From the thyroid gland Baumann extracted a substance containing iodin in organic combination. This he regarded as the active principle and called iodothyrin. This view is open to many objections. Iodin is not found in the thyroid gland of all animals. Thus the gland of a dog fed on meat contains either no iodin or only traces,[2] and in pigs, oxen, and horses, iodin is found very seldom, and then only in minute quantities.[3] Finally Baumann himself states that iodin is not a constant constituent of the thyroid gland in man.[4] We cannot therefore regard the minute amount or the entire absence of iodin in goiters as the cause of this disease.[5] It is possible that the iodin, which exists in small quantities in almost all vegetable food, is withdrawn from the circulation and retained as a harmful substance. In man the administration of iodin or the treatment of wounds with iodoform leads to an increased amount of iodin in the thyroid. Baumann founds his identification of iodothyrin with the active principle on the fact that administration of iodothyrin in goiter causes disappearance of the tumor. But, as Coindet[6] pointed out as early as 1820, this condition has also been successfully treated with inorganic preparations of iodin. In this case however much larger doses are necessary. But it is possible that the organic form may be more readily absorbed and reach the part where its influence is effective. In fact Kocher succeeded in reducing goiters by the administration of an artificially prepared iodin compound of casein.[7] Even before Baumann's discovery, it was known that another artificial compound of iodine—tetraiodopyrrol, had some effect on goiters.[8]

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[1] An account of the comprehensive literature on this subject is given by A. Hirsch, "Handb. d. historisch-geographischen Pathologie," Stuttgart, Enke, Abth. ii. pp. 135 and 136: 1883.

[2] Baumann, *Zeitschr. f. physiol. Chem.*, vol. xxii. p. 14: 1896.

[3] Töpfer, *Wien. klin. Wochenschr.*, p. 141: 1896.

[4] Baumann, *loc. cit.*, pp. 3–12.

[5] Baumann, *München med. Wochenschr.*, No. 14: 1896.

[6] J. Fr. Coindet, *Bibliothèque universelle de Genève*, vol. xiv. p. 190: 1820.

[7] Ed. Wormser, *Pflüger's Arch.*, vol. lxvii. p. 529: 1897.

[8] O. Schorndorff, "Beitr. z. therapeutischen Verwerthbarkeit des Jodes," Diss., Würzburg: 1889.

It is also claimed that good results have been obtained with injections of iodoform.[1] Certain sea animals and plants which contain iodin have been used as medicaments, and especially in cases of goiter, for hundreds of years before the discovery of iodin. Harnack[2] has recently given an interesting account of these iodin drugs. As I have already mentioned, Kocher[3] observed even in the earliest attempts to relieve the struma with thyroid preparations, how much the mode of action resembled that of the long-used iodin. As a final proof that iodothyrin was the active principle of the thyroid, Baumann stated that the tetanic convulsions occurring in dogs as a consequence of thyroidectomy were prevented by the administration of iodothyrin (2–3 grs. per diem).[4] This statement could not however be confirmed by Gottlieb and Wörmser. Gottlieb[5] showed in three experiments that the tetany and death resulting from the extirpation of the thyroid could not be prevented by the administration of iodothyrin. Kocher's pupil, E. Wörmser,[6] comes to a similar conclusion. He finds that iodothyrin was ineffective either in preventing an attack or in stopping an attack which had already begun; whereas all attacks of tetany can be kept off and the life of the animal preserved for a long time by administration of the whole thyroid gland.

All other efforts to isolate the effective principle of the thyroid gland have been equally unsuccessful.[7] None of the substances which have been isolated from the gland have been of any use for counteracting the effects of thyroidectomy. The only preparations which were of any value were those which contained the proteids of the gland, though these were less effectual than the whole gland, dried at 65° C., which in its turn was inferior to the fresh raw gland.

At present there is no evidence against the view that the active principle of the gland belongs to the class of labile proteids, a class including all those substances which have the most

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[1] R. v. Mosetig-Moorhof, *Wien. Press.*, No. 1 : 1890.

[2] E. Harnack, *München. med. Wochenschr.*, No. 9 : 1896.

[3] Kocher, *Correspondenzbl. f. schweizer Aerzte*, vol. xxv. p. 6 : 1895.

[4] Baumann and E. Goldmann, *München. med. Wochenschr.*, No. 47 : 1896. F. Hofmeister, *Deutsch. med. Wochenschr.*, p. 354 : 1896. H. Hildebrandt, *Berl. klin. Wochenschr.*, p. 826 : 1896. A. Irsai, *München. med. Wochenschr.*, p. 1249 : 1896.

[5] Gottlieb, *Deutsch. med. Wochenschr.*, p. 235 : 1896. Compare A. Notkin, *Wien. klin. Wochenschr.*, No. 43 : 1896.

[6] Edm. Wörmser, *Pflüger's Arch.*, vol. lxvii. p. 505 : 1897.

[7] In this connection read : Drechsel, *Physiol. Centralbl.*, vol. ix. p. 705 : 1895 ; S. Fränkel, *Wien. med. Blätter*, No. 48 : 1895; Nos. 13–15 : 1896; J. Notkin, *Wien. med. Wochenschr.*, No. 45, p. 824 : 1895; *Virchow's Arch.*, vol. cxliv.; Suppl., p. 224 : 1896; R. Hutchinson, *Centralbl. f. d. med. Wissensch.*, p. 209 : 1896.

potent influence on the body functions, viz., the most useful ferments and the most virulent poisons. (Compare Lectures XI. and XXVII.)

We may conclude that the assumption that poisonous products of metabolism are destroyed in the thyroid gland must be discarded as extremely improbable. We could not, on such an hypothesis, explain the fact that a very minute fragment of the gland left behind at the operation or transplanted to some other part of the body, is sufficient to prevent all the usual effects of thyroidectomy. Nor does it seem probable that the blood flow through the small vessels of the gland can be sufficiently abundant for such a process of purification to take place to any considerable extent. It is much more probable that the gland is continually giving off to the blood minute quantities of a ferment-like substance, which influences the metabolism in other organs of the body. We thus come to the same conclusion as we arrived at in dealing with the internal secretion of the pancreas. (Compare p. 398.)

Attempts have naturally been made to utilize in therapeutics the various results of chemical and vivisectional experiments described above. The first object of these attempts was to counteract the cachexia strumipriva which supervenes as the result of total extirpation of the gland for goiter. But they were naturally extended to the treatment of myxedema and cretinism. The method first used was that of transplantation of the gland, but it was found that the transplanted gland underwent absorption after a short time, so that only transient improvement was effected.[1] The result was equally unsatisfactory in a case where the human gland itself was used. A female cretin, thirty-three years of age, developed severe myxedema with epileptic attacks and apathy, as the result of total extirpation of the thyroid for goiter. Bircher[2] therefore transplanted into the abdomen of this patient a bit of the thyroid gland, which he had just removed from another patient in an operation for goiter. Within a few days the patient was markedly better, and at the end of four weeks her former intellectual activity and power of work were fully restored. After this came a relapse, and the condition grew steadily worse for four weeks. A second transplantation was therefore carried out in similar manner to the first. Three months after the second transplantation the woman was perfectly well

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[1] Lannelongue, *Wien. med. Blätter*, No. 13 : 1890; P. Merklen and Ch. Walther, *Mercredi méd.*, No. 46 : 1890.

[2] H. Bircher, "Das Myxödem u. d. cretinische Degeneration"; Volkmann's "Sammlung klinischer Vorträge," No. 357, pp. 12–16; and Nachtrag, p. 32 : 1890.

and worked the whole day; but six months later the epileptic attacks recurred. In the same way Kocher[1] succeeded in producing only a temporary improvement in his attempts to treat cachexia strumipriva by transplantation of the gland of men or animals.

It seems therefore that transplantation succeeds only when the transplanted piece of gland becomes vascularized—a process which so far has occurred only in the transplantation in healthy animals when their own gland has been used.

This method had therefore to be given up and trial was made of the introduction of the active principle of the gland by subcutaneous injection or administration by the mouth. The latter mode has proved to be the simpler and more effective. The results have been wonderfully good. The myxedematous swelling diminishes and the general bodily and mental condition improves in a marked manner.[2] Relapse however occurs at once if the treatment be discontinued. Renewed administration of thyroid counteracts these effects for a time, but apparently not permanently, since, as we have already seen in experiments on animals, disturbances of metabolism occur, such as increased output of nitrogen, showing a correspondingly increased proteid disintegration in the tissues.[3] The same result, but to a less extent, follows the administration of thyroid in healthy men,[4] and leads in time to diminished body-weight,[5] and finally to glycosuria[6] and albuminuria.[7]

These experiences have impressed on surgeons the necessity of avoiding where possible complete extirpation of a goitrous thyroid, and the operation is now only performed in certain cases of malignant tumors, such as cancer or sarcoma. Thus the clinical records gleaned by Kocher, Reverdin, and Billroth from cases in which total extirpation of the thyroid in

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[1] Kocher, *Correspondenzbl. f. schweizer Aerzte*, Jahrg. 23, p. 529: 1893; and Jahrg. 25, p. 9 : 1895.

[2] Mackenzie, *Brit. Med. Journ.*, Oct. 29 : 1892. Vermehren, *Deutsch. med. Wochenschr.*, March 16, 1893. Vassale, *Riv. sperimentale*, vol. xix. Fasc. II., III.: 1893. Leichenstein, *Deutsch. med. Wochenschr.*, Nos. 49–51: 1893. Costanzo, *Rivista Veneta di scienze mediche*, vol. xx. Fasc. II.: 1894. Palleske, *Deutsch. med. Wochenschr.*, No. 7 : 1895. O. Lanz, *Correspondenzbl. d. schweizer Aerzte*, Jahrg. 25, p. 296 : 1895.

[3] Mendel, *Deutsch. med. Wochenschr.*, No. 2 : 1893. Napier, *Lancet*, Sept. 30, 1893. Vermehren, *Deutsch. med. Wochenschr.*, No. 43 : 1893. Ord, *Brit. Med. Journ.*, vol. ii. p. 212 : 1893.

[4] Vermehren, *loc. cit.*, A. Dennig, *München. med. Wochenschr.*, Nos. 17 and 20. Bleibtreu and Wendelstadt, *Deutsch. med. Wochenschr.*, No. 22 : 1895.

[5] Reinhold, *Münch. med. Wochenschr.*, July 31, 1894. Bruns, *Deutsch. med. Wochenschr.*, Oct. 11, 1894.

[6] C. A. Ewald, *Berl. klin. Wochenschr.*, Nos. 2 and 3 : 1895. A. Dennig, *loc. cit.* Bleibtreu and Wendelstadt, *loc. cit.*

[7] A. Dennig, *loc. cit.*

man for goiter has been performed, will be of inestimable value for future physiological research, since they can never be repeated.

As already mentioned (p. 441) attempts have been made to treat goiter itself by administration of thyroid gland. Reinhold[1] obtained an almost complete disappearance of the tumor in five cases out of six that he treated in this manner, and Bruns[2] had equal success in nine out of twelve cases. Myxedema and cretinism have also been successfully treated by the administration of thyroid gland,[3] as also by transplantation, though in the latter case the good effects have been only temporary.[4]

The cachexia and bodily and mental weakness, which sometimes supervene after partial thyroidectomy, have also been treated with great success by the administration of raw thyroids.[5]

Finally a large number of the most diverse disorders have been subjected to treatment with thyroid. Among these we may mention obesity, psoriasis, eczema, lupus, syphilis, leprosy, exophthalmic goiter, acromegaly, mental diseases, diabetes, tuberculosis, uric acid diathesis, rickets, &c., &c. It is however impossible at present to say how far this mode of treatment has been of good or of harm in these various maladies.[6]

Before leaving the subject of the thyroid gland, I may mention the observations which point to some connection between the activity of this organ and the sexual functions. Impaired development and retarded descent of the testes has been observed after excision of the thyroid in young animals.[7]

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[1] Reinhold, *loc. cit.*

[2] P. Bruns, *Beitr. z. klin. Chirurgie*, 12, 1894. Compare also Kocher, *Correspondenzbl. f. schweizer Aerzte*, vol. xxv. p. 3 : 1895. O. Lanz, *idem*, Nos. 2 and 10 : 1895. A. Irsai, B. Vas, and Gesa Gara, *Deut. med. Woch.*, No. 28 : 1896. G. Reinbach, *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, vol. i.: 1896. H. Stabel, *Berl. klin. Woch.*, No. 5 : 1896. O. Angerer, *Münch. med. Wochenschr.*, No. 4 : 1896. P. Bruns, *Bruns' Beiträge*, vol. xvi.: 1896.

[3] Beadle, *Lancet*, Feb. 17, 1894. E. Mendel, *Deut. med. Woch.*, No. 7 : 1895. C. A. Ewald, *Berl. klin. Woch.*, Nos. 2, 3, and 30 : 1895. O. Lanz, *Correspondenzbl. f. schweizer Aerzte*, Nos. 2 and 10 : 1895. R. Abrahams, *Med. Record*, April, 1895. Vermehren, "Studien üb. Myxödem," Diss. Copenhagen : 1895. Middleton, *Glasgow Journ.*, Feb. 1896. W. H. George, *Brit. Med. Journ.*, Sept. 12, 1896. Rushton Parker, *ibid.*, June 27, 1896. H. H. Vinke, *Med. News*, No. 12 : 1896.

[4] v. Gernet, *Zeitschr. f. Chirurgie*, vol. xxxix.: 1894.

[5] Angerer, *München. med. Wochenschr.*, No. 28 : 1894. Sonnenburg, *Langenb. Arch.*, vol. xlviii.: 1894.

[6] The literature on this subject will be found in a paper by E. Roos, "Ueb. Schilddrüsentherapie u. Jodothyrin," Freiburg and Leipzig, Mohr : 1897.

[7] A. v. Eiselsberg, *Arch. f. klin. Chir.*, vol. xlix. pp. 216 and 225 : 1895.

Langhans found the testes atrophied in cretins.[1] A connection of the thyroid gland with the sexual functions has been known of for a long time.[2] Swelling of the gland is often observed at the menstrual period as well as during pregnancy, parturition, and lactation, though this does not occur in the majority of cases. Thus J. Fischer[3] could only detect swelling of the thyroid gland in two cases out of fifty during menstruation, and in only one-third of the cases in pregnancy. The more frequent occurrence of myxedema in women is worthy of note. According to the results collected by a committee of the Chemical Society,[4] out of every hundred cases of myxedema, eighty-six are women and only fourteen men. In the ovaries of cretins, Langhans[5] found the follicles but slightly developed; only a few follicles were in a process of growth, while the majority remained in their primitive condition. In the transplantation experiment of Bircher's,[6] which I mentioned above, the awakening of the psychical functions was attended with a restoration of the sexual functions. Menstruation which had ceased for a year, occurred again regularly after the transplantation.

A connection of the gland with sexual life seems to be indicated by the fact to which Schölein[7] draws attention, viz., that the frequency of goiter shows two maxima, one at the time of puberty and the other during senile involution.

An interesting observation has been made on birds by Lanz,[8] who took two young hens of the same brood and in one of them excised the thyroid gland. The operated animal developed more slowly and was smaller than the other. Its comb was also ill-formed. There was also a great difference in the laying powers of the two hens; the one which had lost its thyroid laid only one egg four months after the extirpation. This had a shell as thin as paper and weighed only 5 grms., whereas an ordinary hen's egg weighs 50 to 60 grms. In another experiment Lanz took nine hens, all eighteen months old, and to one of them gave 10 to 30 grms. of thyroid gland every day to eat. While the other eight hens laid altogether

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[1] Th. Langhans, *Virchow's Arch.*, vol. cxlix. p. 155: 1897. The views of earlier authors on the subject of the sexual organs in cretins are quoted here.

An account of our knowledge on this matter is given by H. W. Freund, *Deut. Zeitschr. f. Chir.*, vol. xviii. p. 213: 1883.

[3] J. Fischer, *Wien. med. Woch.*, Nos. 6, 7, 8 and 9: 1896.

[4] *Clin. Soc. Trans.*, supplement to vol. xxi. London: 1888.

[5] Langhans, *loc. cit.*

[6] Bircher, *loc. cit.*, p. 3407.

[7] J. L. Schönlein, "Pathologie u. Therapie," part i. p. 81, St. Gallen: 1846.

[8] O. Lanz, *Mitth. a. d. Kliniken d. Schweiz*, iii. p. 540: 1895.

forty-two eggs in twenty-three days, the ninth that was fed with thyroid laid in the same time sixteen eggs, *i. e.*, three times as many as the others. The weight of these eggs gradually increased; the last egg laid before the thyroid feeding was begun weighed 50 grms., while afterwards the weight gradually rose to 60 grms.

I may now say a few words about the anterior glandular portion of the PITUITARY BODY. The position of this gland renders it extremely inaccessible to operative interference, so that attempts at its removal are usually attended with fatal results from the operation itself and teach us nothing concerning the significance of the organ. The pituitary body has sometimes been found hypertrophied in dogs and rabbits after extirpation of the thyroid,[1] and hypertrophy has also been found in man in sporadic cretinism, accompanying atrophy of the thyroid,[2] as well as in one case of goiter.[3] These facts, as well as the occurrence of iodin in the human pituitary body,[4] have led to the assumption of some analogy between the functions of this body and those of the thyroid.

Rogowitsch regards the pituitary body as equivalent to the thyroid, and emphasizes the fact that rabbits, which withstand the effects of thyroidectomy longer than do dogs or cats, possess also relatively larger pituitary bodies. In the rabbit the thyroid is only three times as heavy as the pituitary, whereas in dogs and cats it is fifteen to twenty times as heavy.[5]

Finally the view has been put forward that disease of the pituitary leads to disorders of nutrition as extensive as those following diseases of the thyroid. Just as the latter leads to myxedema and cretinism, so the abolition of the functions of the pituitary body is supposed to lead to acromegaly, *i. e.*, a morbid increase in the growth of the bones. In fact in some cases and indeed in all since attention has been directed to the point, hypertrophy or disease of the pituitary body has been found post mortem in cases of acromegaly.[6]

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[1] N. Rogowitsch, *Arch. d. physiol.*, 4 Sér., vol. ii. p. 419: 1888; F. Hofmeister, *Beitr. z. klin. Chir.*, vol. xi. p. 2: 1894; L. Blumreich and M. Jacoby, *Pflüger's Arch.*, vol. lxiv. p. 1: 1896, could not confirm this statement as regards rabbits, nor J. R. Ewald and J. Rockwell as regards pigeons, *Pflüger's Arch.*, vol. xlvii. p. 170: 1890.

[2] Bourneville and Bricon, *Arch. d. Neurologie*, 1886.

[3] K. Wolf, *Ziegler's Beitr.*, vol. xiii.: 1893.

[4] Schnitzler and Ewald, *Wien. klin. Woch.*, No. 29: 1896.

[5] N. Rogowitsch, *Beitr. z. pathol. Anat. u. allgem. Pathol. v. Ziegler*, vol. iv.: 1889. Compare H. Stieda, "Ueb. d. Verhalten d. Hypophysis des Kaninchens nach Entfernung der Schilddrüse," Diss., Königsberg, 1889, and *Ziegler's Beitr.*, vol. vii. p. 537: 1890.

[6] P. Marie and G. Marinesco, *Arch. de méd. expérim.*, July 1, 1891. F. A. Packard, *American Journ.*, June, 1892; K. Wolf, *Ziegler's Beitr.*, vol. xiii.:

Unless the methods of vivisection and asepsis make some unexpected advance, we must in the near future await an increase of our knowledge on this point rather from the side of pathological anatomy and clinical observation.

1893. R. Caton and F. T. Paul, *Brit. Med. Journ.*, Dec. 30, 1893. J. Arnold, *Virchow's Arch.*, vol. cxxxv.: 1894. M. Dallemagne, *Arch. de méd. exp.*, vol. vii.: 1895. Comini, *Arch. per le scienze med.*, vol. xv. No. 21, p. 435 : 1896. R. Roxburgh and A. J. Collis, *Brit. Med. Journ.*, p. 63, July 11, 1896. A. Tamburini, *Riv. sperim. di Freniatria e di Med. legale*, vol. xx.: 1896. Ad. Strümpell, "Lehrb. d. speciellen Path. u. Therapie," 10th ed., vol. iii. p. 165 : 1896.

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