REPORTS

ON THE

CHEMISTRY OF THERAPEUTICS.

BY

JOHN G. MCKENDRICK, M.D., F.R.C.P.E., F.R.S.E.,
Lecturer on the Institutes of Medicine, Edinburgh.

I.—PRELIMINARY.

It is the object of these papers to point out and illustrate the influence which a knowledge of the facts and laws of chemical science have, or ought to have, upon the practice of therapeutics.

At present, this department of medicine partakes more of the character of an art than of a science. It is wanting in precision, both as to facts and as to general principles. Many isolated facts have been observed, and even ascertained by special means and appliances to be true, but few generalisations have been made. The backward condition of therapeutics may be partially accounted for by the fact that, until recently, the actions of remedies have not been systematically investigated in the light of physiological research. The actions of supposed remedies have been often loosely observed and registered, much in the same manner as the early physicists investigated the phenomena of natural philosophy. But the recent remarkable development of physiological science, with the aid of chemistry and physics, and the introduction of new methods of observation and of instruments of precision, have rendered it necessary to reinvestigate the actions of all physiologically active substances. This work has been taken up, and is being assiduously prosecuted, by many scientific men both at home and abroad. Many additions to our knowledge have thus been made; and the ultimate result will probably be, not only the adoption of new remedial agents and the abandonment of old ones, but the discovery of general therapeutical laws. When these have been discovered and formulated, therapeutics may claim to be ranked as one of the sciences.

Therapeutics does not mean simply the physiological actions of drugs and of other remedial agents on the healthy body, but their actions in diseased conditions. This affirmation appears self-evident, yet it is often forgotten; and the assumption is made that the action observed by the practical therapist in the hospital-ward will be the same as that described by the physiological investigator in the laboratory. In many cases, it is well known not to be so; and illustrations of this will be given in subsequent papers. It is necessary, therefore, if we wish to establish a rational system of therapeutics, not only to observe and describe the physiological actions of drugs on healthy animals, but also to notice these on animals in a morbid condition. This opens up an extensive field of research—namely, experimental pathology, a department of scientific work now engaging the attention of eminent pathologists, chiefly in Germany. There can be no doubt that, just as anatomy became exact by the use of the scalpel and forceps, physiology and pathology will become exact by the employment of rigid experimental methods of research. The field of experimental pathology is almost entirely a new one. Up nearly to the present time, we have been accumulating facts regarding diseased organs seen in the pathological theatre after the disease had done its worst. These facts relate chiefly to the physical and chemical characteristics of the diseased organ after death. They are of great value; but, in obedience to the law of the human mind, which prompts to the investigation of the causes of phenomena, we must now go a step farther back. We wish to know the preliminary stages of those morbid actions which have produced histological changes, either complete or partial, of the organ, and consequent loss or perversion of function. This can only be gained by experimental inquiry on animals; as the general rule is, that the disease does not destroy life in the human subject during an early stage, and, consequently, there is no opportunity for *post mortem* examination at that stage. By the artificial production of diseased conditions, however, we may study the successive changes in the tissue or organ which lead to a permanently morbid condition. Thus, accurate knowledge will be obtained which will serve as a basis for a new series of experiments as to the actions of remedies. Given certain morbid conditions, artificially produced, how may these be modified by the physiological actions of active substances?

Labour in this direction cannot fail in being well recompensed by the accurate knowledge obtained. Thus, pathology would become a help to therapeutics. The arrangement or classification of the functions of the body for physiological purposes is already recognised as the basis for pathological inquiry; in like manner, well established facts in pathology constitute a basis for scientific therapeutics.

I do not forget, in making these remarks, that before we can found a rational system of therapeutics, we should, as far as possible, become acquainted with what has been called the natural history of disease. As an element in the inquiry, this has been ably put forward by Dr. Rogers, in his work on *The Present State of Therapeutics*.^{*} Many diseases undoubtedly tend towards recovery. The patient would ultimately become well without medicine. The medicine given may have helped towards recovery, or the reverse. Supposing it has helped towards recovery, the effect has been produced by two causes—(1) the tendency towards recovery without the assistance of remedies; (2) the effect of the remedy. It is not easy to say how much is due to the one, and how much to the other. But the remedy may be beneficial in two ways, although it may not materially change sequence in the natural progress of the disease: (1) it may relieve the sensation of pain; (2) it may save time. Few will deny that it is in the power of the skilful therapist to relieve pain; but the question of time cannot be so easily settled. It can only be settled by taking a disease which naturally tends to recovery: the average duration of the disease in a given number of cases not affected by remedies must be noted; next, the average duration of the disease in a given number of cases influenced by remedies must be noted; and, lastly, the average durations of the two sets of cases are to be compared. It is not easy to make such observations as these, even in hospital practice. In private practice it is impossible, because social factors come into play. Hence, we must resort, for assistance, to experimental therapeutics. Many, if not all, of the ailments "flesh is heir to", may be induced in the lower animals. These may be placed in almost exactly the conditions we desiderate; and, consequently, we may be able to institute such comparative researches as will be of the highest benefit to the human race.

Before entering upon the question of the relation of chemistry to therapeutics, the preliminary questions of the relation of chemistry to physiology and pathology must be briefly discussed. Much of what is termed physiological or pathological chemistry is simply the chemistry of substances derived from the dead tissues. When a living tissue is subjected to certain chemical manipulations, it dies, and substances may then be found, such as albumin, globulin, gluten, etc., having specific chemical properties, and which are assumed to have existed in the tissue during life. Of the chemical composition and reactions of living matter, as was long ago pointed out by Fletcher, we know nothing positively; we are acquainted, however, to a limited extent, with the chemical properties of the plasma from which the living matter derives its nourishment, and of the fluids which contain the materials derived from the retrograde metamorphosis or degradation of the living matter after it has performed its functions. Of the exact chemical changes which occur when the living tissues take up nutrient matter from the plasma, we know comparatively little; nor have the successive steps by which living matter passes into dead matter been fully described. But while we may not know these processes with scientific accuracy, it is a great step to be able to analyse the nutrient plasma before it has been subjected to the selective action of the living tissues, and also to examine the chemical nature of those substances obtained from the disintegration of living tissues. By varying the chemical composition of the nutrient fluid, we can vary the amount and character of the retrograde substances. Thus, a large amount of nitrogenous material in the plasma is followed by a large amount of nitrogenous materials excreted. This has been shown by the experiments of Lehmann, Fick and Wislicenus, Parkes, Pavy, and Mahomed. Similarly, the chemical composition of the nutrient fluid affects the condition of the living tissue both statically and dynamically. Thus, a large amount of oxygen in the plasma circulating through a muscle causes it, according to Brown-Séquard and others, to perform more work and to increase in bulk. It is evident, therefore, that the chemical composition of the nutrient fluid affects both the activity and the growth of the tissue itself and the character of the excrementitious products. This fundamental and apparently self-evident truth will be better realised by viewing the living elements of body as proximately obtained from the internal medium or plasma. This plasma Claude Bernard calls the "physiological medium", because materials introduced as food must be converted into it before they can become a constituent of the tissues.

^{*} On the Present State of Therapeutics, with some Suggestions for placing it on a more Scientific Basis. By James Rogers, M.D., formerly Physician to the British Legation and to the Abouchoff Hospital at St. Petersburg. London: John Churchill and Sons. 1870.

Each tissue derives its nourishment from the plasma, molecule by molecule. Bathed in this fluid, the cellular elements of the tissues are, as Bernard says, "veritable aquatic organisms". The internal medium is incessantly fluctuating. Materials are constantly absorbed from without, and are there elaborated and made fit for assimilation. Materials are also constantly thrown into it as products of waste of tissue, and have to be excreted.

Modern scientific investigation has also shown that chemical changes not only occur in the living tissues which lead to their being split up into simpler chemical compounds, but also that certain elements of the food never become truly organised, or incorporated with the tissues, but undergo retrogressive chemical changes, which have an important part to play with reference to the production of heat and mechanical power. As examples of this kind of change, we may take the splitting up of albumin into a nitrogenous portion to be excreted, and into a non-nitrogenous residue, which, by oxidation of its constituents, carbon and hydrogen, produces energy; or the oxidation of fat, or of the carbohydrates (starch, sugar), or of alcohol. It is evident that the due performance of these chemical changes are essential to the health and capacity for work of the individual. It becomes a matter of inquiry how far these processes are affected by morbid conditions, and how far they may be influenced by the actions of remedies.

In this department of physiology, the question is ever present to the mind—how far the vital phenomena of nutrition may be explained by the laws of chemical combination? These phenomena may simply be the results of chemical combination occurring under special conditions of structure, etc.; but of this there is no proof. The phenomena of nutrition differ so widely from mere chemical phenomena, that they must be due to widely different conditions. "We may never know all these conditions; but that analysis will ever resolve them into simple chemical conditions, irrespective of the speciality of their theatre, may confidently be denied."—(*Problems of Life and Mind*, Lewis, vol. i, p. 113.)

The chemistry of nutrition is specially alluded to here, because it appears to me that, when we are better acquainted with it, we will be in a better position to understand the physiological actions of certain remedial agents.

Changes in physiological activity must be produced either by the direct action of substances on the tissue or tissues affected, or by action on the plasma, or elements of the plasma, which nourish the tissues. How are these tissues affected? If the nutritive plasma which supplies them, in normal circumstances, with the materials they require, be affected chemically by the introduction of a new substance (say a substance called a poison), it is evident that the relation between the plasma and the living tissues will be altered. We do not know, in the present state of science, what this alteration may be, or how it is effected. It is possible that, in some cases, the poison may become incorporated with the living matter before it is capable of affecting its vital action. In other cases, the so-called poison may not become part of the tissue, but may interfere chemically with the changes continually taking place between the tissue and the plasma surrounding it. At present much of this is mere conjecture. The field of histo-chemistry with reference to therapeutics requires to be further cultivated, and it appears to me, that the line in which this is to be done, is by observations on the reactions of minute quantities of chemical substances on living lower organisms, such as *Monera*, *Amæba*, *Paramecium*, and other infusoria; and also on the colourless cells of the blood and other masses of bioplasm found in the body. By pursuing this path of work, it is probable we will learn much regarding the actions of drugs on the ultimate living textures which are concerned in nutrition, innervation, and reproduction.

The conclusion at which we arrive is, that we know little regarding the chemical processes occurring in the living body, either in health or in disease, which can be of much service in the practice of therapeutics. But we know that chemical processes do occur which are closely connected with the manifestation of vital phenomena. If such chemical changes do occur, we may reasonably expect to be able to influence them by the introduction of chemically active substances. This opens up another line of inquiry; namely, how far can we produce changes in physiological action by changing the chemical composition of the substance introduced into the body? The answer to this question is not only likely to be of practical service to therapeutics, but it may reflect light on the true character of those chemical changes occurring in the living tissues, the investigation of which is so difficult.

DONATIONS.—Mr. Daniel Thwaites, J.P., has forwarded a cheque for the sum of £424 to the secretary of the Blackburn and East Lancashire Infirmary, which clears off the debt upon the institution.

A SUGGESTIVE INCIDENT WHICH OCCURRED DURING ETHERISATION.

By FURNEAUX JORDAN, F.R.C.S.,
Surgeon to the Queen's Hospital, and Professor of Surgery at the Queen's College, etc.

EVERY surgeon, it may be presumed, desires to use the safest and most effectual anæsthetic. Those who prefer chloroform believe that, in expert hands, it is safe, and has fewer drawbacks than ether. Conceding much on this point, we must not forget that, while narcotisation is everywhere a daily, an almost hourly, need, its induction does not always fall into experienced hands. If, then, anæsthetics must be frequently administered, and administered with variable degrees of judgment and experience, a growing amount of evidence points to ether as the safer anæsthetic.

Recently, I was about to place a ligature on the femoral artery for popliteal aneurism. The patient having been etherised by my colleague Mr. Priestley Smith, who is very familiar with the use of ether, I made the usual incision in the integuments. The patient showed no sign of pain; but I had scarcely completed the incision, when the limb was seized with a marked tremor of the muscles. To clean a large artery with a sharp knife (and I believe, with the late Mr. Syme, that to dissect an artery with a sharp knife is less mischievous than to contuse it with blunt instruments) in a violently trembling limb is not a desirable proceeding. At my desire, more ether was given, but the tremor continued unabated. I again desired that more ether should be given. Mr. Priestley Smith's immediate and significant reply was this: "The man is as much under the influence of ether as it is possible to put him." With the assistance of firm pressure on the muscles of the thigh, I completed the operation; and I may add, that the man has (fourteenth day) done perfectly well.

From the incident just related, a few useful conclusions may be drawn. The most important is this: the profoundest anæsthesia of ether is not so deep as to prevent reflex muscular tremor from following an incision in the skin. It is probably much less profound than even ordinary degrees of chloroform-narcotism. In short, it would seem that, with common care, a patient cannot be put dangerously under the influence of ether. Nevertheless, the anæsthesia of ether is sufficient for the vast majority of operations. Ether, then, notwithstanding certain drawbacks, should claim our first attention.

The chief drawback of ether is, that it cannot be readily administered by timid persons. Anybody can pour a little chloroform on to a handkerchief, and hold it over a face. Not everybody can resolutely pour out a large quantity of ether, resolutely and closely bind a towel round the mouth and nose, and resolutely disregard the most violent muscular contortions. But these are difficulties which very attainable knowledge and experience will surmount.

In a few operations where the skin needs to be freely incised, and especially where such incisions precede delicate and anxious manipulations, the deeper influence of chloroform may be desirable. Quite recently, the practice of beginning with a little chloroform, and then giving ether, answered extremely well in the hands of my colleague Dr. Sawyer in the case of an old man, from whose tarsus I removed a carious patch by means of a large trephine, after a free crucial incision in an "Esmarchised" limb.

In this note, it is far from my intention to discuss the general question of anæsthesia; but a few words, and a few only, on chloroform. I entirely coincide in the opinion, that every kind of "apparatus"—everything containing "valves"—should be scrupulously avoided. Every effort should be made to prevent, what so readily occurs, a deeper anæsthesia than the particular operation, or stage of operation, requires. Timid chloroformisation is, especially in the early stages, equally mischievous. Timidity in the administration of chloroform means much more chloroform, longer time, and greater danger. Again: conjunctival insensibility is too rough a test; it may come too soon. Much worse, it may come too late. In children, the conjunctiva is often insensible in a few moments, especially if there be anything on the stomach. As regards food in the stomach, in hospital practice it is common for mothers, when they are instructed to bring children without breakfast (or other meal) to give them some outrageous compound—beer and fruit, apples and pears, being the commonest—under the impression that these are not a meal, and that the poor child must be "strengthened" for the operation. Occasionally, as in old imbibers, the skin is ready for the knife before the eye tolerates the finger. The deep pinch of an artery-forceps at the seat of the operation is a better test.