the amount of PD^- that is formed, and recent work[4] indicates that sulfonamide potency is a direct function of its protein-combining capacity, then in a series of drugs of various pK's acting in a solution at pH near 7, for example, those of intermediate pK should be most effective. For if the drug is a very weak acid, the number of D^- ions is very small, even though most of them may combine with the acid P to form PD^-. On the other hand, if the drug is a very strong acid, the number of D^- ions would be quite large in a solution of pH 7, but since D^- is weakly basic, little PD^- would be formed. The maximum PD^- concentration, for equal additions of sulfonamide, would be formed by a drug with some intermediate value of pK.

The same considerations apply when one considers a basic sulfonamide such as sulfaguanidine, except that in this case the neutral molecule D can combine directly with the acid P to form PD. For basic sulfonamides the same correlation should exist between pK and potency, except that pK now refers to the equilibrium $HD^+ = H^+ + D$.

This qualitative description is supported fully by a detailed, quantitative consideration of the equilibria involved. Complete details of this treatment will be given in a forthcoming publication. For the present it will be sufficient to point out that the equations finally reduce to the following condition relating the pK of the sulfonamide of maximum activity to the pH of the solution:

$$pK_{HD} = pH - \log \frac{1-f}{f} \qquad (1)$$

where

$$f = \frac{d \ln K_{PD}}{d \ln K_{HD}}, \qquad (2)$$

K_{PD} being the dissociation constant of the enzyme-sulfonamide complex. When f is determined for a given bacterial system, pK_{HD} can be predicted immediately.

Unfortunately we can not make a direct test of this prediction at present, because data for the direct evaluation of f for bacteria are unavailable. Nevertheless, we can evaluate f indirectly for *E. coli* and compare the value so obtained with that derivable from work[4] on the combination of serum albumin with sulfonamides.

Bell and Roblin[1] have found that in a solution of pH 7, maximum bacteriostasis of *E. coli* was obtained with a sulfonamide with a pK of about 6.7. Substituting the appropriate values in (1) we find f is 0.3. Such a value of f is apparently very reasonable if we may compare it with the approximate value derived for serum albumin. From the work of Davis and Wood[4] one can calculate relative values of K_{PD}, for sulfonamides of various K_{HD}'s. A plot of log K_{PD} vs. log (K_{HD}) fits a straight line fairly well and the slope of this line is f. For serum albumin f turns out to be 0.5.

The inhibition of sulfa action by p-aminobenzoic acid is also amenable to the type of treatment described above. In this case we assume that when the ratio of PA^- (the p.a.b.-enzyme combination) to PD^- reaches some fixed value, inhibition sets in. The mass law treatment then predicts that the ratio of the total amount of p-aminobenzoic acid necessary to cause inhibition, to the total amount of sulfonamide present, will be a maximum for the sulfa compound of greatest potency. This is in agreement with the data of Rose and Fox.[5]

Thus, the law of mass action, as applied to a system consisting of a sulfonamide and an enzyme in a buffer solution, predicts the existence and acid dissociation constant of a drug of maximum potency, correlates the effectiveness of basic as well as acid sulfa compounds with their acid ionization constants, and accounts quantitatively for the inhibitory effect of p-aminobenzoic acid.

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CORRECTION

IN a revision of the proof a serious omission was made in the inadvertent dropping of "and 1 ml. of 0.1% $CuSO_4 \cdot 5H_2O$ solution" after "Aliquots of 2.0 ml are mixed with 6 ml of clear 12.5 per cent Na_2CO_3 solution" on p. 405. Addition of copper is essential in enhancing the sensitivity of the Folin reagent, as already noted by others.

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SCIENTIFIC BOOKS

PHYSIOLOGICAL CHEMISTRY

The Dynamic State of Body Constituents. By R. SCHOENHEIMER. Harvard University Monograph in Medicine and Public Health No. 3. 79 pp. Harvard University Press. 1942. $1.75.

THE nineteenth century, which ended about 1914, was the callow age of the physiological chemist. Rudolph Schoenheimer's "The Dynamic State of Body Constituents" marks the transition to a humbler, more realistic and more mature state of mind.

Until recently, the physiological chemist described

[4] Davis, SCIENCE, 95: 78, 1942; Davis and Wood, *Proc. Soc. Exptl. Biol. Med.*, 51: 283, 1942.

[5] Rose and Fox, SCIENCE, 95: 412, 1942.

the animal organism as an engine with a relatively static structure, in which the food was the fuel. A small fraction of the food was used to replace the wear and tear losses of the engine's structure. The working parts of the engine were composed of what was called "protoplasm."

This concept was typical of the era in which thermodynamics with its satellite Newtonian statistical mechanics reigned as the newly enthroned queen of the physical and chemical sciences. It was the era of combustion engines, the era of Helmholz.

The simplicity of the concept of the organism as a combustion engine was, no doubt, one of its attractions. Another was that it helped the physiologists and physicians who were its devotees to feel respectable in the company of the chemists and especially the physicists who were the rigorous, pukka natural philosophers of the nineteenth century.

The concept of the organism as a machine was not a biological concept at all. The physiological chemist knew, or should have known, better. Bernard had demonstrated that the different forms of carbohydrate are maintained *in vivo* in a dynamic steady state and that so long as the animal is alive this steady state can oscillate between only very narrow boundaries. Bernard amplified and generalized the idea into his great concept—"La fixité du milieu intérieur est la condition de la vie libre." Bernard saw clearly, although he had only few examples, that the constancy of the internal environment was a dynamic steady state, and that its constancy was an essential condition of life and was maintained against the impact of wide variations in the external environment.

Outside his laboratory the physiological chemist got himself befuddled by the siren concept of "protoplasm." He knew it is not a substance at all but a conglomerate of many substances; and the idea told him nothing of functional organization. But nevertheless he accepted "protoplasm" as the structural substance of the living combustion engine; the definitive and essential component of "protoplasm" was, of course, protein. This must have been one of the reasons for the welcome which Folin's theory of protein metabolism (first published in 1905) received, and the tenacity with which it has been retained until very recently in the face of accumulating evidence to the contrary over the last thirty years.

According to Folin's theory, the structural parts of the animal body are subject to a continual but small wear and tear and repair. Since the terms "structural," "mechanical" and "protein" were used almost as if they were synonyms, the sum total of changes involved in this wear and tear and its repair was designated "endogenous" protein metabolism. Because the organism was viewed as an engine, and because the structural substance of an engine wears away only very slowly, it followed that only a small fraction of the protein in the food is needed for "endogenous" metabolism. The remainder of the protein in the food, the bulk of it, is quickly hydrolyzed and burned and the fragments excreted. This moiety was designated "exogenous" protein metabolism. Folin's theory was useful; it was based on data which he was the first to obtain, by methods which he had devised or greatly improved. But these data, it is now proved, were misinterpreted, they were forced into the strait-jacket concept of the organism as a combustion engine.

Fat metabolism was viewed in the same context. The bulk of the fat in the body was a depot of storage material, a reserve of energy. This depot was thought to be nearly inert, drawn on only in time of need. Here also there was conflicting evidence, but for the same reasons as in the case of protein metabolism this evidence was ignored.

Schoenheimer and his colleagues at Columbia obtained direct evidence "that all constituents of living matter, whether functional or structural, of simple or complex constitution, are in a steady state of rapid flux." It should be added that the studies of the Schoenheimer group did not deal with carbohydrate metabolism, to which this generalization also applies. Their findings were summarized by Schoenheimer in his 1941 Dunham lectures, and published in this book. The manuscript was prepared for publication after Schoenheimer's untimely death by Dr. Hans T. Clarke and his colleagues.

All these experiments were "tracer" studies. A substance was "marked" with a stable isotope, deuterium, or N_{15}, or both, fed to an animal, and then, from the concentration of the isotope in different body constituents conclusions could be drawn regarding the chemical changes undergone *in vivo* by the substance into whose structure the isotope in question had been incorporated.

Thus with deuterium as a "tracer," it was shown that the fats of the depots are not inert storage materials but that "the fatty acids of the depot fat are to be regarded as being constantly transported, in the form of fats or phosphatides, to and from the organs, where fatty acids are temporarily liberated by rupture of ester linkages. When fat is absorbed, the acids of dietary origin merge with those from the depot, thereby forming a mixture indistinguishable as to origin. Part of the liberated acids are converted into others, whole new ones are steadily formed by condensation of small molecules derived from other substances. Some of this pool of acids is degraded, and

some of it re-enters ester linkages to regenerate fat, which is transported back to the depots. All these complex reactions are so balanced that the total amount and structure of the fat mixture in depot, blood and organs remain constant."

The metabolism of phospholipids deserves a fuller treatment than they are given in this book, especially as we are indebted to isotope studies for nearly all the new and important information on this difficult subject. There is only a cursory sketch of the intensely rapid processes in which the phospholipids are fragmented into their fatty acid, phosphate and choline or ethanolamine components and as rapidly resynthesized.

Essentially the same general picture was obtained of protein metabolism. Here N_{15} was the tracer most commonly used. It was demonstrated that amino acids are continually and rapidly being deaminized and reaminated. Free ammonia is extensively used for reamination. The peptide bonds of the protein chains are similarly continually being broken and reformed. Synthesis of amino acids and protein occurs both when these are abundantly supplied in the diet and when the animal is made to lose weight through inadequate nitrogen in the diet.

It has been argued by die-hard adherents of the older theory that only the so-called "reserve" or "fixed" proteins undergo this rapid disintegration and re-synthesis. Against this argument it was shown that proteins with specific functions, specific antibody proteins, for example, undergo the same rapid synthesis and disintegration as the average immunologically inert serum proteins. Recently it was proved that extensive and rapid resynthesis of protein is continually in progress even in the fasting animal. This and other evidence has destroyed the last vestiges of support of Folin's theory of "endogenous" and "exogenous" protein metabolism.

The important contribution of these studies with isotopes is that they provided direct and incontrovertible evidence for the concept of the organism as a dynamic steady state in which, for the time being at any rate, there is little utility in attempting to distinguish between the chemical changes in the structure of the engine and its fuel. Structural substance and fuel substance are continually interchanging on a large scale and very rapidly.

It is a disservice, however, to the classical pre-isotope methods of physiological chemistry to overlook, as many workers with isotopes and others do, that this concept regarding the proteins in the animal body was enunciated explicitly with a wide variety of supporting evidence before the advent of isotopes.

This criticism applies also to the claims made for the information gained regarding the formation of a variety of amino acids from each other and of urea and creatine. The isotope studies, in most instances, provided only corroborative evidence of facts which had already been firmly established and in more detail by other methods.

In fact, isotope studies have yielded little evidence regarding mechanism. In the two cases they have thrown light on mechanism, the formation of creatine and the transfer of methionine sulfur to form cystine, the same facts were established by direct evidence and in more detail, independently and contemporaneously by non-isotope methods. The latter methods also located the organs in which these changes occur.

The conclusions regarding the dynamic state of body constituents are stated in this book lucidly and eloquently. These ideas are so important that we must regret the book is too short mainly because it is a one-sided account even of the isotope evidence. A broader treatment including earlier non-isotope studies would have shown, on the one hand, more clearly the power of the new tool the physiological chemist has acquired in his use of isotopes and, on the other, the great utility and wide range of the concept of the organism as a dynamic steady state. In contrast to the mechanical nineteenth century concept it has replaced, the new concept is biological. It explains, without strain, the inter-relation between the metabolism of carbohydrate, phosphate and protein, the regeneration of plasma protein, certain aspects of the formation and disappearance of antibodies from the blood, the changing size of organs and muscles in different dietary states. The new concept has given us a view of the organism as a chemical system in which protein, fat, carbohydrate, minerals, vitamins and water are continually and rapidly interacting and yet maintain "la fixité du milieu intérieur" which is "la condition de la vie libre." Our former obscure wonder is replaced by a greater and informed humility and even greater admiration of the marvelous coordination of the complex chemical mechanisms by which living matter sustains itself.

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MODERN PHYSICS

Introduction to Modern Physics. By F. K. RICHTMYER and E. H. KENNARD. Third edition. xv + 723 pp. 234 figures. New York and London: McGraw-Hill Book Company. 1942. $5.00.

THE late Professor Richtmyer's deservedly popular text on modern physics needs no introduction to the reading public. The progress of modern physics has been so rapid during the fifteen years since the first edition was published, however, that frequent revi-