# The Journal of the
# American Medical Association

## Address

### MODERN PROBLEMS OF METABOLISM.*

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Your president has conferred on me a great honor in asking me to deliver one of the opening lectures of the new Harvey Medical Society of this city.

It is your aim that from this well-established center waves of scientific stimulation for research work may arise and reach not only the circles of the professional workers of this city, but even those of the whole country. At this moment, when a society, promoted under such favorable auspices, opens its career by a course of lectures, I think it is opportune, not only to recount the results of investigations already completed, but principally to consider those problems which still await solution.

I am perfectly aware that in doing so I must renounce giving to my hearers the harmonious impression, which a well-worked scheme calls forth; for I am to touch manifold subjects and points of view which stand wide apart and in no organic relation to each other.

Even in confining myself to a very small sphere of the problems of metabolism, a complete and exhaustive representation of such will be impossible. Only a small selection can be made, and even this will savor of arbitrariness.

I may touch, perhaps, on several subjects which to you appear quite unimportant, and, on the other hand, I may omit many points which are of recognized importance. I expressly remark, therefore, that I shall mostly confine myself to questions which enter into my own program for future investigations on the problems of metabolism. If, as a result of my communications, you gain the impression that details of the problems are thrown together by arbitrariness or by chance of selection, I hope that, on the other hand, the personal factor will be the joining link for compensating such disadvantages.

A short retrospect of the history of several problems of metabolism may form a useful preface. All the first investigations, decades ago, were directed toward the recognition of the quality of the chemical changes in the body. The substances, which resulted from the breaking up of the tissues of the body and of the ingested food, were the earliest to be demonstrated. The end-products of animal metabolism were determined. The most important rules were discovered, concerning the production of $CO_2$, urea, uric acid, kreatinin, indican and hippuric acid, etc. Among the normal end-products, many substances were found which appeared only under certain conditions, and were regarded as

characteristic for particular diseases. As examples of such substances I may mention sugar, the various types of albumins, peptone, leucin, tyrosin, lactic acid, cystin, etc. Following this period, in which the names of Wöhler and von Liebig stand out prominently, came the second era, viz., that of pointing out the quantitative changes of metabolism. First introduced by Bischoff, the work in this branch of investigation was carried on and thoroughly established by Carl von Voit and von Pettenkofer and their pupils. Originally confined to the physiologic circumstances in animals and men, this "quantitative study of metabolism" has since obtained new triumphs in its application to clinical medicine and to the study of pathologic processes. It is scarcely twenty years since these investigations commenced, and already, both in the physiologic and in the clinical laboratory, these quantitative estimations are being placed in the background, while attention is being directed to the newer field of the intermediary processes of metabolism. The finest and best work of late years relates to these questions. Hence to-day the investigations on metabolism approach again in character to those of the first period; but what then appeared impossible is now being attacked from all sides. Then one had to be satisfied with a knowledge of the end-products only; to-day one endeavors, through the prominent discoveries in chemistry, to make clear the intermediate stages, through which the metabolites pass to their final conditions. An infinite number of new questions is thus presented by the recent advance in physiologic and pathologic chemistry.

A number of important questions, which are of interest to the physiologist and pathologist alike, however, were left unsolved during the earlier periods of quantitative estimations, and it is only now that—thanks to the better technic of recent times—exact measuring methods are available for their investigation.

First of all, there is the question of the metabolism of energy. Since the time of Voit and Rubner it has been customary to express and to measure body "energy" in terms of calories. In part through the relation of the body weight to the necessary intake of food, and in part from the amount of oxygen consumed and of $CO_2$ expired, certain average figures have been determined. When an adult man is in a condition of complete muscular rest, from 22 to 24 calories per kilo of body weight are necessary during each twenty-four hours; with usual light work, from 32 to 36 calories are required. The daily food must have these calorific values if the weight of the body shall neither increase nor diminish. With the increase of muscular work, the amount of energy consumed increases in certain proportions, and these latter have been sufficiently ascertained. We know also that children require a relatively high, and old people a relatively low, exchange of energy.

Still, all these are only average numbers and they

require the further support of numerous careful and exact observations. Even the most trustworthy figures, obtained by the use of methods, of whose accuracy there is not the slightest shadow of doubt, showed that under exactly the same conditions a difference of from 20 to 25 per cent. arose between single individuals; this can only depend on the so-called individual factors. In future, however, this difference may not be slurred over by the use of the mystic word "individuality"; we must endeavor to make clear the reasons for the rise above the average in oxidative processes in one person, and the fall below the average in another. Such information would provide us with a clear—I might even say a mathematical—insight into the condition which we now designate by the term "individuality."

An important by-question which arises in regard to the physiology of nutrition, is the problem of the influence exerted on the consumption of energy by the respective constituents of the food.

Certain experiments which Max Rubner and Ed. Pflueger have carried out on animals, tend to show that when the food contains an excessive quantity of proteids the energy-exchange rises considerably above the average. The energy production appeared to rise higher than was necessary for the muscular work done and for the maintenance of the body warmth. These results remind one of the old theory known by the name of "Luxus-consumption," if even it does not entirely compass it. They are too few and insufficient to revive the old hypothesis, which we have long known to be erroneous. As, however, one of the bases of the new science of nutrition is touched by it, the point should be thoroughly cleared up by new and better experiments on human subjects. If the excess of proteid intake really exerts a marked influence on the oxidative processes of the human organism, then we must change many of our views and explain differently a number of former experiments in metabolism. Up to now we trust that not the kind and the amount of food but only the internal and external bodily work rules the extent of the oxidation. The question is not a theoretical one only. Recently manifold endeavors have been made to shake the old standard numbers for the albumin intake of healthy men settled by the school of Voit for these endeavors, which originated from the supporters of vegetarianism, it would be water on their mill if it were proved, that large amounts of albumin raised the consumption of energy to an unseemly, that is to say, to an unnecessary and prodigal, extent. The theory of vegetarianism would also receive a specially strong support were it possible to confirm the oftspoken assertion that the prodigal expenditure of energy only follows an excessive intake of animal albumins and does not result from a similar quantity of vegetable albumins. A few experiments we made lately turned against the theories of Rubner and Pflueger.

Of greatest interest and importance are, of course, those alterations of the exchanges of energy which occur in various diseased conditions. Single and occasional former investigations excluded, we first commenced only about ten or fifteen years ago to busy ourselves with these matters. One single important fact is thoroughly established, viz.: The increase of the energy exchange which follows the administration of thyroid gland substance. This observation, which was made in my clinic by my former assistant, Prof. A. Magnus-Levy was suggested by the practical experiences of Yorke-Davies and Leichtenstern on the influence of thyroid gland tablets on obesity. Later, Mag-

nus-Levy discovered a similar increase in the transformation of energy in exophthalmic goiter and a decrease in myxedema. But these are the only diseases in which, up to now, spontaneous changes in the output of energy are known to occur. Thus the studies—I might call them preliminary—which have hitherto been made on the extent of the processes of oxidation and the amount of nutriment necessary in diseased conditions, afford sufficient reason for the use of our improved methods in further investigations in this field. Many of these problems are of great practical importance for bedside treatment. Next, there is the old question of how great the metabolism energy is in people who are run down by chronic disease or by insufficient nourishment. Do these persons require the same amount of food as do healthy individuals, reckoned per kilo of body weight, or do their bodies diminish the extent of exchange on some self-regulated plan? It is certain that the albumin metabolism is diminished. It has even been asserted that the total production of energy also is diminished, but on this we are as yet without definite proof. My preliminary observations point to the contrary, but the question has not yet been investigated with scientific exactitude. The extremely painstaking and brilliant work of Neumann in Kiel, and of Chittenden in America, which has demonstrated the surprising extent to which the food of an adult man may be diminished without affecting the capacity for work and without altering the nitrogenous equilibrium of the body, leaves untouched this particular question.

Obesity is quite the contrary. For a very long time it has been asserted that there are two forms of obesity. One type is said to result from an excessive intake of food or from insufficient muscular exercise; the other is said to arise from an endogenous retardation of metabolic exchanges. The question is of great theoretical interest, but, as every one must admit, it is also of marked practical therapeutic importance. Since I first approached the matter, some twelve years ago, by investigations on the respiratory exchanges, the question has been constantly discussed. Some differences exist between the results of clinical observation and of laboratory experiments. Clinical reports indicate the occurrence of cases in which the obesity is due only to abnormal lowering of the oxidation, that is, to a diseased state of the protoplasm. Scientifically exact experiments, however, have failed to discover such relations. The results of some work done in the clinic at Basel seemed to point to abnormal low oxidative changes during muscular work and during the digestive processes of obese persons, but they must be discounted by the fact that the methods of estimation employed were not free from objections; correct deductions from them are therefore impossible. I am convinced, however, that with the advent of more satisfactory methods the views of the practitioners will be confirmed by laboratory experiments.

Since the earliest days of investigations on metabolism, the question as to the energy exchanges in fever has received attention. That the albumin exchanges are increased is quite certain; toxic influences are the reason. But why does the patient waste during the periods of fever? Why does he also lose so much of his body fat? As a matter of fact, in every case of long-continued fever, we observe an enormous loss of weight, even if we endeavor to avoid this loss by the administration of rich and nutritious foods. Does the cause lie in the fact that in spite of all our care an individual can not ingest the normal average calories

of the food, since the digestive organs during fever are unable to take in or to digest the necessary amount? Or do the oxidative processes in the fever periods rise markedly above the normal? If this is the case, the food requirements of the fever patient will not be satisfied by ordinary quantities; the amount of food sufficient for a healthy individual would not prevent the patient wasting during the stages of fever. The practitioner of earlier times did not doubt that fever was always accompanied by a substantial increase in all the processes of oxidation. The exact investigations on metabolic changes which have been made during the last decades do not, however, confirm these ideas. These consist, in particular, of the works of Senator and some investigations by F. Kraus and by the pupils of Zuntz. If we thoroughly and critically read through these works, we find that they are full of contradictions and by no means permit of any final conclusions being made. The technic of to-day promises, however, a satisfactory and objection-free solution of this old problem. Still, the working out of the matter is naturally dependent on clinical material, and, unfortunately, the majority of hospitals to-day are not equipped with the necessary apparatus.

Among other diseases, in which the energy exchanges should be further investigated, I may mention diabetes mellitus. In slight cases, the relations are simple and undisputed. Such cases do not exert any influence on the energy exchanges.. For a long time, however, it has been supposed—and lately the assertion has been revived on many sides—that in severe cases of diabetes the production of energy, and consequently the food requirements, are distinctly diminished. It has been calculated that in these patients the daily energy needs are satisfied with from 18 to 20 calories per kilo of body weight, while the healthy person requires from 34 to 36 calories under parallel conditions. The question is of great practical importance, because a clear conception would be of real assistance to us in the difficult dietetic treatment of diabetes mellitus. I do not allow the just-mentioned figures, concerning the diminished production of energy in severe cases of diabetes, to be quite correct; and I am of the opinion that the few previous exact observations on the production of $CO_2$ and the consumption of oxygen, are quite sufficient to prove this. Anyone who possesses a large respiratory apparatus, can definitely settle the entire question in a few days.

We leave now those questions which are intimately connected with the transformation of energy, and turn to another very interesting and important problem, relating to the metabolism of albumin. Earlier experiments on animals and recent investigations on human subjects have taught us that an excessive amount of food compels a retention of nitrogenous substances in the body. The usual nitrogenous equilibrium is disturbed; a smaller quantity of nitrogen appears in the excreta than was present in the food. This retention of nitrogen may be attained by the administration of large amounts of albumin, but much more thoroughly and surely by a simultaneous excess of fat or especially of carbohydrates. The albumin-sparing properties of the two latter substances, of course, are well known. The ultimate effect of such overnutrition is always an increase in the total quantity of fat. We apply this knowledge therapeutically in our "feeding cure," etc. But regarding the nitrogen there was until a short time ago the opinion that in spite of such an excessive nutrition, the nitrogen retention was only slight in quantity and short in duration—at least so far as well-nourished

adults are concerned. It was taught that the body always endeavors to maintain a nitrogenous equilibrium so that, in the case of over nutrition while the excess storing of fat may continue for a long time, a similar storing of proteids is soon stopped. In certain cases, however, the storing of body proteids seemed to be both extensive and long continued, as for instance, during the period of body growth, or after chronic exhaustive diseases, or after periods of lowered nutrition—it is always during the new growth of tissues. The occurrence of considerable nitrogen retention has recently been noted, apart from the conditions just mentioned. In a case of my own, I found that in two months not less than 370 grams of nitrogen were retained. Expressed in terms of meat this is more than 11 kg. of flesh. Is this retained nitrogen really built up into pure albumins and protoplasmic substance? Our general knowledge tends to indicate otherwise. We know that excessive feeding produces obese, but never athletic, individuals. A priori, it is very improbable that the nitrogen retained during excessive nutrition indicates the formation of pure albumins or a new formation of tissue substance. Perhaps the nitrogen only exists in the form of nitrogen-containing fragments of the large molecules of albumin, which are held for a time and are then cast off at a later period. In favor of this supposition there is the fact, that when the period of excessive nutrition is stopped, it is usual for an enormous quantity of nitrogen to appear in the urine.

The exact form in which the nitrogen is retained within the body is still, however, entirely unknown. It is, nevertheless, an important question, because a knowledge of it would throw light on the changes which the molecules of albumin undergo in the body.

This problem leads us by easy paths to the consideration of the intermediate stages of metabolism, which is the special field of modern physiologic chemistry.

Naturally, most questions of the "intermediary" metabolism concern themselves directly or indirectly with the fate of the albumin molecules; with their disintegration as well as with their synthesis. It seems that the synthesis of albumin in the body may originate from much simpler molecules than we could conceive of until lately. By intense and long-continued tryptic digestion of albumin, the latter has been broken up until the solution no longer yields the biuret reaction. In spite of this, the administration of the products of such digestion to animals, served for the substitution of pure albumins and for the maintenance of nitrogenous equilibrium.
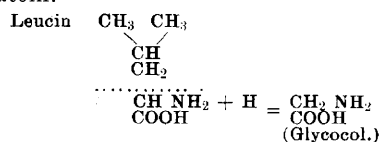
In close theoretical relation to this brilliant and important experiment of Otto Loewi stand those considerations, which are bound up with the discovery of erepsin in the walls of the alimentary canal. This ferment splits up the albumoses and peptones into simpler substances and, in particular, splits off the amino-acids. Hence, it has been assumed, that this action represents the regular arrangement of processes, that the organism normally lives on the amino-acid mixtures, and that from these basal substances are formed the albumins which ultimately circulate in the blood stream. Such a sweeping conclusion, however, is a little too previous, for it has been shown recently that erepsin occurs in all the organs of the body and thus is not specific for the alimentary tract. The ferment, which *in vitro* is able to split up the albumoses when acting in the intestine may, synthetically, form albmumoses from amino-acids. Such reversibility of ferments is already known. These considerations appear to indicate, there-

fore, that the real function of the intestinal mucosa is not to break up the albumoses into amino-acids, but, on the contrary, to build up albumoses and similar substances out of the amino-acids, which pass into the intestinal wall from the lumen. The question is certainly an available one for further experimental investigations. First of all, the living and surviving intestinal mucosa must be allowed to act on a mixture of amino-acids. This experiment has not yet been made. It is one, of course, which is very important for our ideas concerning the assimilation of albuminous substances. If the investigation yielded positive results, there would be a remarkable analogy between this process and that of the synthesis of fat by the intestinal cells. Concerning the fate of fats, we know (1) that a fat-splitting ferment (lipase) is present in the intestinal wall; (2) that by the aid of this ferment there also occurs in the intestinal wall a synthesis of fat from fatty acids and glycerin; (3) that *in vitro* this synthetic process can be reproduced by the aid of lipase. For these brilliant and important investigations we are indebted to your own countryman, Dr. Loewenhardt.

These questions are of great significance in practical dietetics, since they bring into greater application the until now almost entirely neglected amino-acids. In particular, rectal feeding would receive a new impetus. Among the amino-acids there are many substances which are less irritable to the mucosa of the large intestine and are more easily absorbed than the usually prescribed albumoses and peptones. We have already commenced investigations on this point.

Associated with the amino-acids, which represent the chief nitrogen-containing group of the albumin molecules, are many other questions, only a few of which can be touched on here. The chief of my clinical laboratory, Dr. G. Embden, has lately made an investigation on the amino-acids under physiologic and pathologic conditions. What I have to say on this point is due chiefly to the important theoretical and analytical work of Dr. Embden.
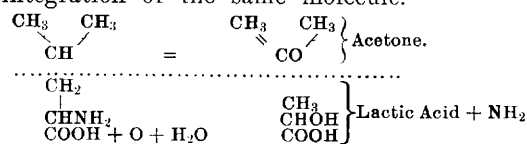
First, I have to mention that glycocol probably can be split off from all the amino-acids, the chains of the higher constituted amino-acids being broken up between $a$ and $\beta$ C-atom.

$$\text{Leucin} \quad \begin{array}{c} CH_3 \quad CH_3 \\ \diagdown \diagup \\ CH \\ CH_2 \\ \cdots\cdots\cdots\cdots \\ CH \; NH_2 + H \\ COOH \end{array} = \begin{array}{c} CH_2 \; NH_2 \\ COOH \\ \text{(Glycocol.)} \end{array}$$

This process, it would appear, plays a great part in the organism. Recent investigations in my laboratory have shown that glycocol is normally present in all urines, and in such quantities as to approach up to 1 per cent. of the total nitrogen output. This well-grounded observation is striking, because we have for a long time known that glycocol introduced into the stomach is very easily assimilated and reappears as urea in the urine. The formation of glycocol within the body must be very large, if the kidney is able to catch and to eliminate some portion of it. This production of glycocol from the higher amino-acids may also explain how it is that the body always has glycocol at its disposal for coupling or combination purposes. I recall to mind the instances of hippuric and glycocolic acids. Further experiments must be performed, however, in order to determine whether or not the administration of large quantities of the higher amino-acids is followed by the appearance of a supernormal amount of glycocol in the urine.

If the formation of glycocol from the higher amino-acids takes place in the manner which our preliminary investigations suggest as being probable, then a new light will be shed on the question of the formation of sugar from albumins. Since it has been established that higher amino-acids, such as alanin, form a definite source for sugar (G. Embden and H. Salomon), G. Embden, working in my laboratory, has shown that after the removal of the pancreas in dogs, sugar is formed from glycocol equally as it is from alanin and other higher amino-acids. Glycocol seems to be one of the most prolific sources of sugar that we know of. This fact, taken in connection with the previously mentioned conditons of glycocol formation out of other amino-acids, explains at one stroke the question of sugar formation from albumins, and effectively removes those objections which have been heard during the most recent years.

Glycocol, however, does not seem to be the only amino-acid from which sugar can be rapidly formed. Our attention has also been directed specially to leucin, for the reason that of all the amino-acids leucin occurs most largely in the majority of the proteids of food. We are quite certain that lactic acid can be produced from alanin, and that in fact this procedure takes place within the body. A similar possibility obtains for the formation of lactic acid out of leucin. Theoretically, on the addition of water and oxidation, leucin breaks up into acetone and lactic acid, while at the same time amides are split off. Attention only just recently has been drawn to how often this process occurs in the chemistry of animal tissues and how important it is. In this case the chain of C-atoms is broken between the $\beta$ and $\gamma$ atom. You see, there are different possibilities of disintegration of the same molecule.

$$\begin{array}{c} CH_3 \quad CH_3 \\ \diagdown \diagup \\ CH \\ \cdots\cdots\cdots\cdots \\ CH_2 \\ | \\ CHNH_2 \\ COOH \end{array} + O + H_2O = \begin{array}{c} CH_3 \quad CH_3 \\ \diagdown \diagup \\ CO \end{array} \Big\} \text{Acetone.} \quad \begin{array}{c} CH_3 \\ CHOH \\ COOH \end{array} \Big\} \text{Lactic Acid} + NH_2$$

In confirmation of these theoretical possibilities, we have just proved that the "surviving" liver always excretes some acetone into perfused blood, and that the amount of acetone considerably increases when leucin is added to the inflowing blood. At the same time, as we have determined with certainty the formation of lactic acid from leucin, we are met with a new problem, associated with the as yet unknown changes during the passage of carbohydrates through the body. We certainly know the end-products of carbohydrate disintegration—carbonic acid and water—but in regard to the intermediary metabolism of carbohydrates and the manner in which those end-products are produced we are still in the realm of theories. Entirely disconnected facts are alone our guides. One of the earliest theories related to the formation of lactic acid from carbohydrates; but until now no satisfactory proof of this was given to us, at all events so far as muscular tissues are concerned. Many physiologists consider the lactic-acid formation in muscle to be due to postmortem changes. The modern technics, which have advanced perfusion methods to a remarkable extent, will make possible a definite solution of the problem; until now, it is only solved so far as the liver is concerned. In my laboratory, Embden and Almaggia have thoroughly demonstrated that lactic acid ensues in fact from disintegration of carbohydrates by the liver. This result arises from the action of a ferment and, as all our experiences with organic ferments indicate that the action of these

ferments is reversible, so this procedure may also take place in the reverse way. As a matter of fact, we know that very often the administration of lactic acid to individuals affected with severe diabetes, and more especially to dogs after removal of the pancreas, is followed by an increase in the glycosuria. We also consider lactic acid as a rich source of glycogen. These few available facts lead to the following hypothesis:

A part of the sugar which is broken up in the muscle circulates in the blood as lactic acid; the lactic acid passes to the liver and is there rebuilt up to carbohydrate and eventually reaches anew the muscles in the form of sugar. With this conception of the intermediary stages and circulation of the carbohydrates in the form of lactic acid, some well-known facts are in full agreement. After extirpation of the liver, sugar disappears from the blood stream and lactic acid makes its appearance. Another remarkable fact may also be explained on this hypothesis. When the pancreas is removed from birds, glycosuria does not result. In these animals, lactic acid is not bound to be regenerated into sugar, but with the addition of ammonia, it can form uric acid. If this view be a correct one, then the uric acid of the bird is partly a derivative of sugar. I advance this theory, of course, only in the form of an hypothesis; it has, in any case, the advantage of promoting further investigations on the intermediary stages of carbohydrate metabolism and of providing a new aim and a definite proposition for further proof.

I have already mentioned that, theoretically, acetone may be produced from leucin, and that we have been able to demonstrate this procedure by experiments on animals. This result is very remarkable, since the opinions of to-day designate the fatty acids alone, and the lower fatty acids in particular, as the source of the acetone bodies, and because until now we have always accepted the oxybutyric and diacetic acids as the necessary precedents to acetone. This latter view thus requires correction, although our experiments in no way show that in the formation of acetone leucin plays an important figure in respect to quantity. At all events, it indicates that the acetone question can not yet enter into a condition of rest. Also the problems of the formation of acetone from fat and the hindrance to the production of acetone through the simultaneous oxidation of carbohydrate, are still sufficiently enigmatical and can not be solved until we know much more about the intermediary disintegration of fats and of carbohydrates than we do up to this day.

With this I wish to conclude my survey of modern problems of metabolism. As I stated at the commencement of the lecture, it has been necessary to roam over a large amount of ground and to consider subjects that were but slightly related to each other. You will observe that to-day we are busying ourselves in a much more intimate manner with the details of metabolic processes than in not very remote periods was deemed either necessary or possible. Already the little that has been mentioned here is more than the working powers of one single man can master; but on all sides we see new young energy pouring into this interesting and important branch of medical investigation, in order to harvest this inexhaustible field. We greet them with joy and with satisfaction. The results will not be long in coming.

We are all convinced that these marked steps into the wonderland of animal metabolism will not only advance the theoretical science, but, as we have always seen, that every advance in physiologic and pathologic chemistry has been followed by improvement of our bedside treatment. The achievements of the dietetic treatment of diseases have gone hand in hand with the advances in theoretical investigations. If we compare the progress in dietetics that has been made during the last decade with the wonderful successes of the surgeon, the medical clinician no longer need feel either shame or envy. In the same period a vast amount of work has been done by the internist in regard to therapeutic matters. The close relations which have been maintained between the progress in clinical bedside treatment on the one hand and physiologic and pathologic chemistry on the other, has been very fruitful indeed, and still fruitful will remain.

Great problems still await solution and rich outside help is necessary thereto. With confident expectation, medical science looks to this country, in which in recent times numerous ardent and honest research-loving young workers have entered into the service of problems of metabolism, and in which the riches and the munificence of its inhabitants more than elsewhere have provided that external aid which has made more easy the prosecution of great and far-reaching investigations. I close with the prophetic words of our Goethe:

> Amerika, Du hast es besser
> Als unser Continent der Alte.

## Original Articles

### COCCIDIOIDAL GRANULOMA.*

W. OPHÜLS, M.D.
SAN FRANCISCO.

We have in California a peculiar form of oidiomycosis of which, so far, no cases have been described in people who had not been in our state, except the very first case of this form of infection which was observed by Wernicke[1] in Buenos Ayres and later more accurately described by Posadas. The first case in California was reported by Dr. E. Rixford[2] of San Francisco to the San Francisco Medico-Chirurgical Society, March 4, 1894. Another similar case under the care of Drs. Thorne[3] and Robinson was seen by him[4] the same year. Later Dr. Rixford,[5] in conjunction with Dr. Gilchrist of the Johns Hopkins Hospital Medical School, gave a more complete description of these two cases and of the parasite.

This description established fully the morphology of the parasite in the tissues and the nature of the lesions which it produces. At that time, however, the organism was looked on as a protozoon, on account of failure to obtain growths, and on account of a certain resemblance to the coccidia named *Coccidiodides immitis pyogenes resp.*, the idea being that on account of some morphologic differences the parasites in the two cases might not be the same. This view of the animal nature of the parasite proved to be erroneous in the course of the examination[6] of a new case of this disease which oc-

* From the Pathological Laboratory of Cooper Medical College, San Francisco.
* Read in the Section on Practice of Medicine of the American Medical Association, at the Fifty-sixth Annual Session, July, 1905.
1. Wernicke: Centralblatt f. Bact., 1892.
2. Occidental Medical Times, 1894, vol. viii, 326.
3. Thorne: "A Case of Protozoic Skin Disease." Occidental Medical Times, 1894, vol. viii, 703.
4. Rixford: "A Case of Protozoic Dermatitis." Occidental Medical Times, 1894, vol. viii, 704.
5. Rixford and Gilchrist: "Two Cases of Protozoan (Coccidioidal) Infection of the Skin and Other Organs," Johns Hopkins Hospital Reports, vol. i.
6. Ophüls and Moffitt: "A New Pathogenic Mould." Philadelphia Medical Journal, 1900.