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CONTRIBUTIONS OF THE CHEMIST TO OUR KNOWLEDGE OF BIOLOGICAL OXIDATIONS[1]

THE contributions of the chemist to our knowledge of biological oxidations are today of such magnitude that they constitute a subdivision of biochemistry. A mere enumeration of the problems which have been solved would be of little purpose; on the other hand, to speak at length on a few interesting details would be evidence of lack of appreciation of the great contributions which have been made. I shall therefore try to point out the methods by which the various types of investigation have been carried out rather than give great detail concerning any one investigation.

CALORIGENIC RELATIONSHIPS

The problem of the oxidation of foodstuffs may be considered from the standpoint of the three classes of compounds, carbohydrates, fats and proteins. The calorigenic relationships were placed on a firm basis when it was shown that the same amount of heat was produced whether glucose was burned in the body or in a bomb calorimeter. Studies in the complicated apparatus necessary for direct calorimetry have now given way to the analysis of expired air, and for most work all the essential data may be obtained by indirect calorimetry.

After it had been shown that 1 gm. of glucose, 1 gm. of fat and 1 gm. of protein furnish to the animal organism 4.2 calories, 9.46 calories and 4.3 calories, respectively, it was realized that all the essential data required to estimate the diet requirements of an animal organism were at hand. These data, however, furnished no information concerning the mechanism by which glucose, fats and proteins were burned in the animal organism.

INTERMEDIARY METABOLISM

Despite the large amount of work carried out in the field of intermediary metabolism many important questions remain unanswered. Embden and Meyerhof have shown that glucose apparently is utilized through the decomposition of a hexose phosphate, and the work of Hill and Meyerhof is very suggestive that at least a portion of the lactic acid is burned to

[1] Presented as part of a symposium on "The Contributions of Other Sciences to Medicine" at the annual meeting of the American Association for the Advancement of Science, Nashville, December 28, 1927.

carbon dioxide and water. This detail of the combustion of glucose has not, however, been proved, and Lusk has placed an interrogation point after this portion of the Hill-Meyerhof theory. It is possible that other substances are burned in place of lactic acid.

There is also the question whether glucose can be burned by any mechanism in the animal organism other than through the course of phosphoric acid ester, lactic acid, carbon dioxide.

Thunberg has shown that succinic acid is readily attacked by enzymes in the muscle, and the significance of this observation in relation to the combustion of sugars, proteins and fats is not clear.

Other problems relating to the oxidation of glucose deal with the phenomenon of antiketogenesis. Is sugar necessary for the proper combustion of fat in the animal organism? Shaffer and coworkers and others have indicated that it is, and have suggested a stoichiometric relationship. On the other hand, it has been suggested that ketone bodies are formed when the quantity of fat utilized is raised above a certain level. If glucose is burned in preference to fat the addition of carbohydrate to the diet would relieve the ketogenesis, but by a different mechanism than that suggested by Shaffer.

Still another problem in the oxidation of glucose is the specific dynamic action of this material. Lusk has shown that a plethora of glucose produces an increased rate of utilization of this sugar, and Woodyatt has shown that continuous injection of glucose results in an increased rate of the oxidation of this material.

The combustion of fats is still shrouded with mystery. The one most important fact in the oxidation of fat is the evidence concerning the point of attack in a fatty acid; this was shown by Knoop. A long chain of carbon atoms terminating in a carboxyl group can be burned in the animal organism by the successive breaking off of groups of two carbon atoms at a time, but the details of this decomposition and the fate of the two carbon atoms is still unknown. Meissl and Strohmer, Voit and Lehmann and Lusk have shown that glucose can be converted into fat and it seems probable that the combustion of fat can be utilized for the production of mechanical energy in the body, but no one has yet conclusively shown that fat can be converted into glucose. The problems to be answered in this field are closely bound up with the fatty-acid-containing substances of the body, such as lecithin, cephalin, fatty-acid esters of cholesterol and other substances, some of which are insoluble in water, and yet are absorbed through the intestine and transported in the blood.

The combustion of the proteins involves the added problem of the fate of the nitrogen-containing substances. Some of the amino acids in protein can be converted into sugar and are probably burned as glucose; some apparently can not be converted into glucose but follow a separate path. Knoop has suggested that ketone acids and ammonia can interact with the formation of amino acids through the aid of the sulphydryl group of glutathione which functions as a reducing agent.

The influence of proteins on cellular activity has been investigated for many years. Through the work of Voit, Rübner, Lusk and many others it has been shown that the administration of proteins and certain of the amino acids results not only in the combustion of these substances but also in an increased rate of oxidation of other metabolites. This occurs in the phlorizinized dog, even though the carbon content of the amino acid is quantitatively excreted as glucose. The specific dynamic action of proteins is one of the most interesting and important phases of oxidation in the animal organism.

Probably the most important problem in the oxidation of glucose, fats and proteins is the relationship of glucose to other carbon compounds. It is hoped that the investigation of intermediary metabolism will eventually explain the conversion of glucose-forming substances to sugar and bring into harmony the theories concerning the utilization of carbohydrates, fats and proteins for the production of heat and energy.

FOOD ACCESSORIES

After it had been shown that a diet should contain carbohydrate, fat and protein, it was assumed that any normal animal organism would grow to maturity and enjoy normal health provided a sufficient number of calories of a well-balanced diet was furnished. The satisfied feeling which accompanied this conclusion was rudely jarred about fifteen years ago by the discovery of a group of substances which were termed food accessories, or vitamins, that appeared to be essential for the proper growth and maintenance of health in the normal animal organism.

This problem is with us to-day and one receives at least an introduction to these substances through the columns of the daily newspaper or the popular weeklies. I shall not discuss in detail the influence of the vitamins on the oxidation in the animal organism, but shall call attention to three substances which appear to be related, at least in their action, to the so-called food accessories.

Throughout the period during which biological oxidations have been investigated each successive decade has given its own peculiar contribution to the problem, and the investigators who have taken up this work in turn have doubtless felt that until some un-

suspected door was opened, further progress with the problem would be but meager.

The physicist of 1895 could not visualize the magnitude of the regeneration which would follow the discovery of radioactivity and the better understanding of electromagnetic vibrations. The biochemist in 1895 did not realize that he would soon look down a long avenue through a door which had just been opened to permit a partial view of the problems and triumphs which were to come.

During the few years preceding 1895, the attention of clinicians was strongly attracted to the striking results obtained by feeding the thyroid gland to human beings and experimental animals deficient in thyroid function, and in December of that year Baumann published the important discovery that iodine was a normal constituent of the thyroid gland. Because of the clinical importance of this work it was soon followed by a more detailed investigation and in a relatively short time Magnus-Levy showed that administration of the thyroid gland increased the rate of oxidative processes in the body. I shall not at this time outline the isolation of thyroxine and the subsequent developments in this field.

About twenty-five years ago through the efforts of Abel, Takamine, Aldrich, Lucius, Brüning and Flächer, the first crystalline compound from a gland of internal secretion was isolated, identified and synthesized and it was soon shown that epinephrin or adrenaline affected physiological processes to a marked degree. Many years passed, however, before Boothby, Marine, Means, Soskin and others showed that in this case also at least a portion of the effect is due to a change in the rate of oxidation.

Through the efforts of still a third group of investigators, Hottinger, Thunberg, Meyerhof, Hopkins, Dixon, Tunnicliffe, Voegtlin and others, another agent of great significance in biological oxidations was recognized and finally isolated, identified and synthesized, glutathione.

The isolation and identification of these compounds, however, did not mark the completion of the problem. The chemical properties and effects of these three compounds and related substances will occupy the attention of investigators for many years.

The first step necessary was to determine the end results brought about by the administration of these compounds. Careful determinations of the basal metabolic rate and of the intake and output of nitrogen, sulfur, calcium, etc., have been made and quantitative relationships have been determined concerning the effect of thyroxine.

The influence of adrenaline on blood sugar, carbon dioxide output and oxygen consumption has been shown, and the influence of glutathione on oxidation in vitro and on muscle tone has been studied. These results deal only with the end products of reactions which are irreversible within the animal organism. It was recognized that energy had been generated by a combination of the oxygen of the air with hydrogen and carbon of the food, but the mechanism by which thyroxine, adrenaline or glutathione brought about a change in the velocity of oxidative processes has remained up to the present time an unsolved problem.

The problem is complex and must be approached through the efforts of investigators from many different points of view. The processes influenced by these agents take place in a colloidal medium where surface tension, phenomena of adsorption, the selective action dependent on stereoisomerism—and the commanding influence of hydrogen-ion concentration affect the mechanism involved. The equilibrium which exists is delicately balanced.

It is obvious that the tissues can not be in a state of static equilibrium. Even at rest chemical processes are continually occurring and the problem involves a kinetic equilibrium which is influenced by innumerable factors.

Oxidation-Reduction Potentials

Before the work of van't Hoff, Arrhenius, Ostwald, Sorenson, Clark and others the relations between amphoteric substances and hydrogen-ion concentration in biological phenomena were not appreciated. The early workers in the field of biological oxidations were not cognizant of the static and kinetic equilibriums which exist between oxidizing and reducing agents and the velocity of the reactions associated with life processes. By the use of oxidizing dyes many qualitative results were obtained and attempts were made to determine the intensity of oxidation in the animal organism, but the actual progress made toward this objective was but meager until still another avenue of approach for a quantitative study of the oxidation-reduction intensity was opened by Clark and coworkers.

This group of investigators has made a great contribution to our knowledge of oxidation-reduction potentials, and now for the first time the investigator in oxidation-reduction processes is equipped not only with an adequate theory concerning the mechanism involved but furthermore with a series of dyes which have been studied with precision so that the intensity of oxidation of any given solution can be determined within narrow limits.

This painstaking investigation has opened for the biochemist of 1927 a wide entrance to a fertile field; before the end is reached biological oxidation will be intimately linked with simpler systems by means of a fuller understanding of the physico-chemical prin-

ciples involved. The processes occurring in the tissues, which are described to-day as enzyme action, will be explained in terms of thermodynamics to a degree which has been up to the present wholly unattainable.

The problem of biological oxidation was presented by Hopkins in 1926 at the International Congress of Physiologists. He reviewed the two theories: activation of oxygen suggested by Warburg and others, and primary dehydrogenation suggested by Wieland and others. The dehydrogenation theory of Wieland was favored by the essayist, although it was evident that probably a middle ground would eventually afford the correct interpretation of the phenomena.

Clark has shown that the intensity of oxidation or reduction of organic dyes is related to the structure of the dye and he has proposed a theory of the mechanism of oxidation-reduction processes which is broad enough to include the essential features of both those of Wieland and of Warburg. This theory expresses the oxidation and reduction of complex organic dyes in the same terms employed to describe the reaction involved in the oxidation or reduction of inorganic compounds such as ferrous and ferric salts. In the words of Clark:

> Oxidation may be regarded as the withdrawal of electrons from a substance with or without the addition of oxygen or elements analogous to oxygen or as a withdrawal of electrons with or without the withdrawal of hydrogen or elements analogous to hydrogen. Reduction is the reverse of oxidation as defined above.

This definition meets on common ground with the definition of an acid and a base given by Lewis:

> A basic substance is one which has a lone pair of electrons which may be used to complete the stable group of another atom, and that an acid substance is one which can employ a lone pair from another molecule in completing the stable group of one of its own atoms. In other words, the basic substance furnishes a pair of electrons for a chemical bond, the acid substance accepts such a pair.

When the phenomena of biological oxidation are investigated with this broad viewpoint, both in respect to the nature of oxidizing and reducing substances as well as acid and basic compounds, the nomenclature and the significance of the chemical reactions involved form a continuous pathway from the complex field of biological oxidation through to the realm of simple water solutions containing only inorganic substances. Such a theory has proved adequate up to the present and, by excluding the question of whether or not hydrogen is added or removed during the processes of oxidation and reduction, has eliminated an unnecessary and superfluous detail.

To insist upon the addition or removal of hydrogen but complicates the problem. Clark has pointed out that because hydrogen is associated with a reductant when removed from solution is not evidence that the hydrogen is actually a component part of the compound as it exists in solution. However, the theory that the reactions are dependent on the transfer of electrons from those substances which can furnish electrons, or the acceptance of electrons by compounds that can accept them furnishes a viewpoint which will satisfy the broadest requirements of the problem, at least for many years.

Oxidation Characteristics of Adrenaline and its Derivatives

The beautiful experiments of Gesell on control of respiration have been made possible by the development of methods for the determination of the relationship between oxygen, the oxidative rate in the tissues and the hydrogen-ion concentration in the living animal organism. Means has also reported the effect on the circulation of changes in the basal metabolic rate due to the administration of thyroxine and adrenaline. An investigation has been carried out in my laboratory, with E. J. Witzemann, which carries our knowledge of the chemical reaction involved back one step further and has brought to light some chemical characteristics of adrenaline and glutathione which have been demonstrated in simple buffer solutions.

Throughout this work it was assumed that the surface of the platinum electrode indicated the concentration of electrons from the substances in the solution which could be regarded as reducing agents, and that the oxidation-reduction potential indicated by the platinum was the algebraic sum of the influence of available electrons and the effect of the total oxidant in the solution. The compounds related to adrenaline can be divided into three groups: (1) ephedrin, (2) adrenalone, and amino and dimethylaminoacetopyrocatechol, (3) adrenaline, the methyl and ethyl ethers of adrenaline and the anhydride of adrenaline.

The first problem investigated was whether these substances can be reversibly oxidized. It was quantitatively shown that ephedrin could be neither oxidized nor reduced at a pH 7.4 with any of the oxidizing dyes used, with or without the presence of molecular oxygen or hydrogen peroxide. Adrenalone and its two derivatives act as reducing agents toward dibromophenolindophenol and indigo carmine and can be reversibly oxidized; adrenaline and its three ether derivatives are all oxidized by dibromophenolindophenol, but are not oxidized by indigo carmine. However, when the compounds in Group 3 are

oxidized, the molecule is so altered that the solution does not contain any oxidizing substances. The end products of mild oxidation of adrenaline, therefore, may be described as irreversible.

The results of this part of the investigation have established certain characteristics of these substances which are of the greatest significance: first: the velocity of oxidation and the degree of oxidation are not determined by the intensity of the oxidizing agent used; and, second, before adrenalone and its derivatives can act as reducing agents some intermediate addition complex must be formed which activates the compound and permits it to function as a reducing agent.

The first conclusion is clearly shown by the velocity of oxidation of adrenalone and its derivatives with dibromophenolindophenol, methylene blue and indigo carmine. Indigo carmine has an almost specific effect on the molecule and the presence of 5 per cent. of one equivalent of indigo carmine markedly increases the velocity of oxidation with dibromophenolindophenol. Such a result is contrary to the usual velocity of oxidation induced by these dyes.

When molecular oxygen is passed through a solution of adrenalone dissolved in phosphate buffer, pH 7.4, no oxidation of the adrenalone occurs. If, as assumed by Wieland, hydrogen is first removed from the molecule then adrenalone can not spontaneously act as a hydrogen donator in the presence of molecular oxygen, or in the terms of Clark we can conclude that electrons can not be withdrawn from the adrenalone molecular with molecular oxygen. The same stability of the molecule is exhibited toward hydrogen peroxide. Furthermore, adrenalone does not appreciably affect the platinum electrode, which indicates that adrenalone can not affect the concentration of electrons in a solution at pH 7.4. However, if to such a solution 5 per cent of one equivalent of indigo carmine is added, the dye is rapidly reduced, and the platinum electrode indicates a marked reduction potential. If, as well as the indigo carmine, molecular oxygen or hydrogen peroxide is added there is a cyclic oxidation and reduction of the indigo carmine resulting in the oxidation of the adrenalone. This effect of adrenalone is evidence for the second characteristic which I have attributed to this substance and can be explained on the assumption that some type of addition compound is formed between indigo carmine and adrenalone: the result of this reaction is the liberation of available electrons.

Two other observations were made: (1) Indigo carmine is reduced by adrenalone even in the presence of an excess of hydrogen peroxide. Hydrogen peroxide added to a solution of reduced indigo carmine results in the rapid oxidation of the dye, but in the presence of adrenalone oxidation of the reduced indigo carmine occurs but slowly.

(2) The formation of some addition complex between adrenalone and the oxidizing dye is indicated by the addition to the solution of a compound which does not have oxidation-reduction power itself, but which inhibits the oxidation of adrenalone by the oxidizing dye. Such a substance is tungstic acid. If but a small percentage of one equivalent of tungstic acid is added to a solution of adrenalone in phosphate buffer, pH 7.4, there is no change in hydrogen-ion concentration, but the velocity of oxidation with dibromophenolindophenol or with indigo carmine is reduced almost to zero. It can not be assumed that the amount of tungstic acid in the solution caused an oxidation of the reduced form of the dye, and the reaction is adequately explained by the assumption that the formation of an addition complex between adrenalone and the dye is prevented by the presence of the small amount of tungstic acid. No precipitate is formed in the solution.

The effect of oxidizing dyes on adrenalone is similar to the effects of oxidizing dyes on other biological products. As Oppenheimer points out, nothing occurs in these cases except that the hydrogen is taken up by the acceptor and then the leuco dye formed turns it over to the oxygen. He concludes by saying, "This is the fact, the explanation is not available."

The results which I have outlined indicate that actual addition products are formed in the solution.

The necessity for a consideration of the chemical configuration of an oxidizing dye is strikingly shown by the influence of dibromophenolindophenol, methylene blue and indigo carmine on dimethylaminoacetopyrocatechol. This compound reacts sluggishly with dibromophenolindophenol, but if indigo carmine is added to the solution the velocity of oxidation is markedly increased. The discrepancy reaches its maximal proportions when methylene blue is used. This dye is not reduced by dimethylaminoacetopyrocatechol, but if a small percentage of one equivalent of indigo carmine is added to the solution prompt reduction of both dyes occurs. This is evidence that the formation of an addition complex is essential for the interaction of this group of compounds with oxidizing dyes.

If addition complexes between adrenalone and metabolites can be formed in the animal organism, it is possible that this reaction explains in part the marked effect of this series of compounds on the oxidative process in the animal organism. It therefore became desirable to show that a similar reaction occurs with adrenaline. Toward oxidizing dyes adrenaline reacts in a manner closely simulating that of

adrenalone, except that it is entirely stable toward indigo carmine.

Experiments showed, however, that adrenaline does not function as an oxidizing agent after it has been partially oxidized with a dye. This was eventually shown to be due to the fact that one portion of the adrenaline molecule is too unstable to remain unaffected by the oxidized portion of the molecule. The result of the interaction of the two portions of the adrenaline molecule is the loss of all oxidizing power which can be transferred subsequently to another substance. This suggested the possibility of demonstrating the cyclic oxidation and reduction of adrenaline, provided some substance was present which would reduce oxidized adrenaline before one portion of the adrenaline molecule reacted with the oxidizing group. Adrenalone will serve this purpose. If air is passed through a solution of adrenaline the adrenaline is oxidized. If air is passed through a solution of adrenalone there is no effect. If air is passed through a solution of adrenalone containing a small amount of adrenaline the adrenalone is oxidized and then, and only then, will the molecular oxygen destroy the adrenaline. The presence of adrenalone, therefore, prevents the adrenaline molecule from reacting with itself, and the net result of the reaction is the oxidation of adrenalone.

This reaction, however, is not quite so simple. It will occur provided a fourth compound is present in the solution, but the presence of such a substance is essential. Such a compound is present in a solution of glucose which has been oxidized with molecular oxygen in the presence of alkali and indigo. The chemical groups which are necessary are unknown, but, in the presence of this compound, molecular oxygen will oxidize adrenalone provided adrenaline is also present. The results are quantitative and striking, and emphasize the necessity for the presence of these four substances before this reaction can take place.

This indicates the delicately balanced equilibrium which must be present, and further indicates the necessity of the formation of addition products before oxidation can occur.

OXIDATION-REDUCTION POTENTIALS OF GLUTATHIONE

Still further evidence concerning the formation of addition complexes has been secured by Nord in the oxidation of glutathione. In the absence of oxygen or sulfur, glutathione and cysteine can not reduce indigo carmine; if, however, oxygen is admitted to a solution containing cysteine and indigo carmine or if a small percentage of one equivalent of sodium disulfide is added to such a solution, prompt reduction of the indigo carmine occurs; moreover, the solution is capable of reducing further additions of indigo carmine.

If such a solution is boiled the cysteine or glutathione present can no longer reduce indigo carmine, and finally the actual oxidation-reduction intensity of the solution is determined by the ratio of –SH to the –SS groups which are present in the solution. These results are explained by the formation in the solution of thermolabile oxygen or sulfur addition products between indigo carmine and cysteine which activate both the –SH and –SS groupings.

These results indicate that the –SS grouping is capable of exerting an oxidizing influence, and, although such power of the –SS grouping is absent in a simple phosphate buffer solution, in the presence of the oxygen addition product the –SS grouping of cystine or oxidized glutathione will oxidize reduced indigo or reduced indigo carmine.

The demonstration that the activity of glutathione is dependent on the presence of thermolabile unstable addition products containing oxygen and sulfur suggests that the biological significance of these compounds depends upon the presence of similar substances in the animal organism. Investigation of the activity of the –SH and –SS forms of glutathione in vivo has shown that the condition in which these substances exist depends on the metabolic changes occurring in the muscles, liver and kidneys.

The potentiometric investigation of the activity of these compounds furnishes a glimpse of that complex, ever-changing series of reactions which is occurring in vivo and upon which physiological processes are dependent.

NECESSITY FOR ACTIVATION

The determination of the oxidation-reduction potentials of the derivatives of adrenaline is conclusive evidence that these substances are not of themselves powerful reducing or oxidizing agents and that they must be activated by other substances in the tissues of the animal organism before they can influence the intensity of the oxidation-reduction processes involved.

Dixon has suggested that the –SH group of cysteine dissociates even in a simple phosphate buffer with the liberation of hydrogen and the formation of cystine. The results reported in this communication indicate that before the –SH group can function as a reducing agent with sufficient intensity to reduce indigo carmine the sulphydryl grouping must be activated by the presence of some type of oxygen addition product.

These results emphasize the importance, in biological processes of oxidation, of addition complexes which appear to be essential for the functioning of at least adrenaline and glutathione. The activating

influence of oxygen or its chemical equivalent has not been appreciated, largely because the experimental methods employed have not adequately excluded oxygen from the sphere of reaction. With properly controlled experimental technic it can be shown that oxygen occupies a unique position concerning the oxidation-reduction power of cysteine and glutathione. This action is not concerned with the oxidizing power of oxygen but with the activation of the sulfur atom in the presence of thermolabile oxygen addition products so that the –SS and –SH groups can manifest their latent powers of oxidation and reduction.

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MAYO FOUNDATION

CONTRIBUTIONS OF ANTHROPOLOGY TO MEDICINE[1]

IN the first number of the *American Journal of Physical Anthropology* for this year, I had occasion to point out the intimate and direct relations of anthropology with medicine and to show, briefly, what medical men, more particularly the anatomists, have done for anthropology. On the present occasion I want to call attention, equally briefly, to what anthropology has done for medicine.

The subject will, I think, be at once clearer and more sympathetic to you when I remind you that anthropology, in a large measure, is merely the daughter and a continuation of the medical sciences. The best and briefest definition of physical anthropology that we are able to arrive at to-day is that it is the human *phylology* of the past, the present and the future. More in detail it is, first, the science of human origin and evolution, or of human phylogeny; second, it is the comparative science of the human life cycle from its inception to its end or human ontogeny; and third, it is the science of human variation. All of which means merely that it is human biology, and advanced, comparative, human anatomy, physiology, chemistry and even pathology.

The distinctive feature of anthropology and the one that separates it most from the regular medical sciences is its *comparative* nature. It deals not with the characters and manifestations of an abstract or average human being, as do the medical branches, but studies human groups, whether they be age, sex, racial, social, occupational or even abnormal groups, comparing them with others. As to "practical" application there is the difference that medicine tries essentially to restore the damaged or diseased goods, while anthropology endeavors to find and to show the harmful as well as the favorable means for further human evolution. Anthropology, with much justice, could be called the medicine of human groups.

Being what it is, it must be quite plain to all of us that indirectly or directly the bulk of the research in physical anthropology is of more or less value to medicine. That medicine does not or can not as yet make fuller use of anthropological knowledge is quite another matter, related to its similar inabilities in respect to biology, physics and even chemistry; it is the difficulty of assimilation. It may be said at once, however, that medicine is already using many results of anthropological research without being always conscious of the source.

Let us approach the concrete facts. Research in physical anthropology began materially in the fifties of the last century. The register of printed anthropological articles and books since then reaches many thousands.

Taking the card catalogue of these publications in my division, I find that over 50 per cent. of the titles are direct contributions to comparative human anatomy, physiology or pathology. A few examples may elucidate this further. Let us take, quite at random, the three items of "skull," child" and "pelvis," and see the nature of the anthropological studies under these heads:

Skull	Children	Pelvis
Anomalies	Abnormalities	Age changes
Architecture	Backward	Anomalies and abnormalities
Asymmetries	Births, multiple, etc.	Anthropological differences
Capacity	Brains of defective	Deformations
Capacity vs. stature in defectives	Development	Dimensions
Deformations	Dimensions	Evolution in fetus and child
Development and growth of distinguished men and women	Infanticide	Ossification
Evolution	Pathology, comparative	Sexual characters
	Pulse, respiration, temperature	Variation

Practically every more civilized country has already one or more periodicals devoted largely or entirely to physical anthropology. Let us take the first page or two of the index of the oldest of these journals, the *Bulletin* of the Anthropological Society in Paris, and we find such items as these:

Abdomen: (racial differences in the muscles of);
Acclimatization;
Accouchement (childbirth), among different peoples;
Achondroplasia;
Acrocephaly;
Acromegaly;
Agraphy;
Albinism;
Alcoholism, and depopulation, criminals, suicides;
Algiers—demography, psychology;
Alienation, mental, and the brain, etc.

[1] Presented as part of a symposium on "The Contributions of Other Sciences to Medicine" at the annual meeting of the American Association for the Advancement of Science, Nashville, December 28, 1927.