lies," write Moore and Purinton,[109] "should be avoided in any method devised for the isolation of the active substance, since the activity is thereby rapidly destroyed." As Moore[110] has previously stated that alkalies supplemented by heat also caused oxidation of the reducing agent in adrenal extract, melanin should likewise actively take up oxygen through alkalies, if the kinship really exists: Jones refers to several experiments in which ammonium permanganate was used as oxidizing agent, at temperatures between 0° and 5° C. "Even under these conditions," says this chemist, "the permanganate is almost immediately decolorized, showing that in alkaline solution the *pigment is oxidized with the greatest ease.*"

This not only clearly connects melanin with the adrenal secretion, but it does so with the adrenal secretion as a constituent of the albuminous body. Indeed, we have seen that the sulphur in hæmoglobin belongs to the latter only, and that, as shown by Sieber[111] and Hirschfeld,[112] melanin also contains sulphur.

Still, if melanin contains the adrenal secretion, the latter should also contain sulphur. The active principle of the adrenals contains no sulphur, the formula of adrenalin being $C_9H_{13}NO_3$. The *secretion,* however, which embodies the active principle, contains this element. Manasse[113] found it in the glandular substance. Metzger[114] also obtained it from adrenal precipitates. Gurber[115] found that adrenal substance gave off sulphur in the form of sulphuretted hydrogen when heated to 140° C. Sulphuretted hydrogen was also obtained by Schmiedeberg,[116] from melanin.

Additional evidence is afforded by the fact that melanin is precipitated from its solutions by agents which act similarly on adrenal extracts. Just as Vulpian, fifty years ago, found the expressed juice of adrenals insoluble in alcohol, ether and benzene, to which list others have added chloroform, so does Arthur Jones refer, in his recently published paper, to an acid

[109] Moore and Purinton: Amer. Jour. of Physiol., vol. iii, p. xv, 1900.
[110] Moore: Jour. of Physiol., vol. xvii, p. xiv, 1894-95.
[111] Sieber: Archiv f. exp. Path. u. Pharm., Bd. xx, S. 363, 1886.
[112] Hirschfeld: Zeit. f. physiol. Chemie, Bd. xiii, S. 418, 1889.
[113] Manasse: Zeit. f. physiol. Chemie, Bd. xx, S. 478, 1895.
[114] Metzger: Inaug. Dissert., Giessen, 1897.
[115] Gurber: Sitz. d. physik. med. Gesellsch., Wurzburg, Bd. xxix-xxx, S. 139, 1897.
[116] Schmiedeberg: Arch. f. exp. Path. u. Pharm., Bd. xxxix, S. 2, 1897.

preparation (adrenalin is not destroyed in acid solutions) of melanin obtained by him, as being "insoluble in alcohol, ether, benzene, acetic ether and chloroform."

Again, several chemists have assimilated the chromogen of the adrenals to pyrocatechin, a substance found in mucin, the urine, etc., and which, precisely as Vulpian observed in the case of adrenal juices, gives an emerald green color with ferric chloride and other characteristic tests. Krukenburg[117] suggested that the chromogenic substance contained pyrocatechin. Brunner[118] found that an alcoholic extract of adrenals gave practically all the reactions of this body. Mühlmann[119] likewise concluded that pyrocatechin was present in the adrenals, and observed that just as pyrocatechin became brown when exposed to light or to the action of alkalies, so did adrenal extractives. He held, therefore, that, inasmuch as the latter were powerful reducing agents, the adrenal secretion on entering the arterial blood became oxidized and turned brown. This, he thought, accounted for the bronzing of Addison's disease. That this view is erroneous is obvious; for our arterial blood would, in that case, be oxidizing constantly the adrenal secretion irrespective of the presence of Addison's disease. Again, since this disease is associated with a destructive lesion of the adrenals, it would tend to prevent bronzing, rather than cause it.

Yet, Mühlmann's conception, as interpreted from my standpoint, embodies the main feature of the process of bronzing, *i.e.,* that it is *a product of the adrenals which, on becoming oxidized, turns brown* in Addison's disease. What is the nature of this process?

We have not far to seek. Since bronzing occurs only in the advanced stage of Addison's disease, and the pigment of bronzing appears in the blood after removal of both adrenals, it is evident that we are dealing with a general lowering of the blood-pressure such as that which occurs, as shown by Strehl and Weiss, when the adrenal veins (through which the secretion reaches the general circulation) are clamped. This means relaxation of all the vessels, a torpid circulation and passive

[117] Krukenburg: Archiv f. path. Anat. u. Physiol., Bd. ci, H. 3, S. 542, 1885.
[118] Brunner: Schweizer Wochen. f. Pharm., Bd. xxx, S. 121, 1892.
[119] Mühlmann: Deutsche med. Wochen., Nu. 26, S. 409, 1896.

infiltration into the cutaneous elements of blood-plasma containing oxidizing substance. All functional processes being torpid, absorption of the exudates is delayed and may even be arrested in tissues supplied by the diminutive capillaries of the surface, where the circulation is at best sluggish. It is here that the pigment accumulates, *i.e.*, in the epidermal layers, where it may become oxidized by what oxygen the fluids in which it bathes may contain or oxygen derived from the air. The presence of sulphur, iron and other elements in the surrounding tissues may so influence the process as to give rise to various hues—those witnessed in various cutaneous disorders. A similar process may occur in any organ.

We have seen in the third section that exposure of oxidase to the air was followed by a similar process and that juices derived from the skin of batrachians first became brown, then black. Osler[120] states that in Addison's disease "the coloration ranges from a light yellow to a deep brown or even black." Harlow Brooks's[121] case of extreme anæmia attended with disease of both adrenals, in which there was a "dark brown, *glossy* pigmentation" of the skin also recalls the process of lacquer formation with the oxidizing substance of the latex tree, *i.e.*, laccase, as described by Bertrand. In both these two extremes of organic life—man and plant—the reducto-oxidizing body had ceased to circulate in its normal channels, and, becoming oxidized, was converted into the substance which in man produces "bronzing."

On the whole, the following conclusions seem warranted: (1) *that bronzing is due to an accumulation of melanin in the epidermal layers of the skin;* (2) *that melanin is a compound formed when oxidizing substance, i.e., the albuminous portion of hæmoglobin, has become vicariously oxidized in any organ (hæmatoidin) or in the skin;* (3) *that the constituent of oxidizing substance which becomes oxidized, when melanin is formed, is the adrenal secretion;* (4) *that whereas melanin is formed in any part of the body, the adrenal secretion circulates in all parts of the body.*

[120] Osler: "Practice of Med.," p. 831, 1898.
[121] Harlow Brooks: Med. Rec., Feb. 22, 1902.

THE ACTIVE PRINCIPLE OF THE ADRENAL SECRETION AS THE ACTIVE AGENT OF THE OXIDIZING SUBSTANCE.

To render all the evidence submitted so far conclusive, the actual presence of the active principle of the adrenals in the oxidizing substance, *i.e.*, the albuminous portion of hæmoglobin, should be demonstrated.

The minuteness of the dose of adrenal that will provoke marked effects suggests that it is as an active principle that it must carry on its important function. "In order to produce a maximal effect," says Schäfer,[122] "a dose of not more than fourteen-millionth of a gramme of the active material per kilo of body-weight is all that is necessary. Now it is certainly true to say that one-fourteenth of this dose will produce some effect, although not, perhaps, a very large one. We thus arrive at the astounding conclusion, that the active principle of the suprarenal capsules, administered in the proportion of not more than one-millionth part of a gramme per kilo of body-weight, which would be equivalent to $^1/_{13000}$ gramme (less than $^1/_{800}$ of a grain) for an adult man, is still sufficient to produce distinct physiological results upon the heart and arteries." The activity of minute doses has been emphasized also by the experiments of Moore and Purinton[123] and Reid Hunt.[124]

Even these diminutive doses perceptibly influence tissue-metabolism. Oliver and Schäfer[125] refer to a slight, transitory "disturbance of the body temperature." When the doses are lethal the latter falls, but after large doses there is a distinct rise. Reichert[126] observed an elevation of 1° F. in rabbits, accompanied by increased metabolism. Lépine[127] states that the increase of blood-pressure is always followed by a rise of temperature. Morel,[128] in four guinea-pigs noted a rise of from $^1/_2$° to 1° C. (0.9° to 1.8° F.). This is controlled by the well-known phenomena that follow removal of both adrenals. Lowering of the temperature was first noted by Brown-Séquard, and since by practically all experimenters. Vassale and Zan-

[122] Schäfer: "T. B. of Physiol.," vol. i, p. 957, 1898.
[123] Moore and Purinton: Amer. Jour. of Physiol., vol. iii, p. xv, 1900.
[124] Reid Hunt: *Ibid.*, vol. v, p. vii, 1901.
[125] Oliver and Schäfer: Jour. of Physiol., vol. xviii, p. 230, 1895.
[126] Reichert: Univ. of Penna. Med. Bull., Apr., 1901.
[127] Lépine: Semaine méd., Feb. 18, 1903.
[128] Morel: Le progrès méd., Aug. 3, 1903.

frognini[129] observed it even during the prolonged post-operative life insured by leaving a portion of the medullary substance intact and *in situ*. Finally, as is well known, hypothermia is a marked symptom of Addison's disease.

If the oxidizing substance, whether linked with the coloring matter as in higher animals, or not, as in the colorless blood of invertebrates, actually contains the active principle of the adrenals, this principle should be found in the blood-plasma. Its presence therein was shown by F. Battelli.[130] As observed by Oliver and Schäfer, Langlois and others, the effects of adrenal extract only last three or four minutes—a fact which led to the belief that it was destroyed in the blood. Such was found by Battelli, however, not to be the case: Normal blood was rapidly centrifugalized. The serum thus obtained was acidulated, subjected to a temperature of 85° C. (which, as we have seen, destroys all active agents except the oxidizing ferment) and concentrated by pressure. One cubic centimeter of this serum invariably raised the blood-pressure. That this was due to adrenal substance was shown by the fact that the concentrated serum was rendered inert by precisely the conditions that affect adrenalin similarly, *i.e.*, oxidation by exposure to the air, and variations of activity on exposure to sunlight, diffuse light and darkness. Quantitative experiments, moreover, showed that "normal *serum* in the dog contains adrenalin in the proportion of 1 in 10,000,000 to 1 in 20,000,000." This is exclusive, of course, of that contained in the hæmoglobin which had remained in the corpuscles.

We have seen that the minuteness of the dose of adrenal extract that will produce distinct physiological effects is referred to by Schäfer as "astounding," its administration "in the proportion of not more than one-millionth part of a gram per kilo of body weight" to an adult man being "sufficient to produce distinct physiological results upon the heart and arteries." In the more recently discovered active principles we have far more powerful agents even than Schäfer employed in his experiments. Indeed, Reid Hunt[131] obtained the following effects with Abel's active epinephrin sulphate:—

[129] Vassale and Zanfrognini: Riforma Medica, Oct. 31, 1902.
[130] F. Battelli: C. r. de la Soc. de biol., vol. liv, p. 1179, 1902.
[131] Reid Hunt: Amer. Jour. of Physiol., vol. v, p. vii, 1901.

	Rise of blood-pressure
0.083 millionths of a gram per kilo body weight . . .	5 mm. Hg.
0.23 millionths of a gram per kilo body weight . . .	7 mm. Hg.
0 49 millionths of a gram per kilo body weight . . .	15 mm. Hg.
0.69 millionths of a gram per kilo body weight . . .	20 mm. Hg.
1 7 millionths of a gram per kilo body weight . .	24 mm. Hg.
5.7 millionths of a gram per kilo body weight . . .	66 mm. Hg.

"These results show," according to Hunt, "that epinephrin sulphate is many times more powerful than the *aqueous extracts* of the medulla of the suprarenal obtained by Moore and Purinton." As adrenalin is at least as active as epinephrin sulphate, the proportion of the former active principle found in the plasma by Battelli corresponds with its "astounding" activity, especially when we consider that in Hunt's experiments, the quantities mentioned were *added* to that already present in the blood of the animals used.

The fact that such minute quantities prove active is, from my standpoint, of great practical importance, since, as shown in the first volume, and as will be further emphasized, many of the effects of drugs, poisons, and toxins are in reality due to the fact that they indirectly stimulate the adrenals, and by thus causing these organs to increase the proportion of their secretion in the blood, correspondingly raise the blood-pressure, hasten metabolism, etc.

That the blood-plasma contains the adrenal active principle is shown by considerable experimental evidence.

In the first place, it is evident that as previously shown, the adrenal secretion as the constituent of the oxidizing substance circulates in all parts of the body. This is demonstrated by the additional fact that it is found in *shed* blood in combination with other constituents of the plasma, *i.e.*, in fibrin.

Gamgee, as we have seen, found that very little was known as to the true nature of the albuminous constituent of hæmoglobin, that to which I traced the adrenal secretion. He states, however, that "the most interesting observations on the *albuminous* products of the decomposition of oxyhæmoglobin" were published nearly forty years ago by Kühne,[132] who showed that "when CO_2 is passed through solutions of pure oxyhæmo-

[132] Kühne: "Lehrbuch," S. 206, 207, 1868.

globin a flocculent precipitate is thrown down which does not possess, as had been erroneously asserted by A. Schmidt, *fibrinoplastic* properties."

In the light of recent experimental work, however, Kühne's observation is subject to a different interpretation. M. Arthus[133] refers to the blood coagulation as follows: "We know that the conversion of fibrinogen into fibrin, the fundamental phenomenon of coagulation in the blood, is caused by the action of a diastatic agent, fibrin ferment, thrombine, or plasmase, produced by the leucocytes in the blood withdrawn from the vessels." In the first volume I advanced the view that the body which converted fibrinogen into fibrin *extra corpore* was in reality the oxidizing substance and that leucocytes absorbed some of the latter to carry on their own functions. Now Abelous and Biarnès[134] found that *"dilution and a current of carbon dioxide precipitate the oxidizing substance"** from saline solutions of fibrin. This conclusion was based on the fact that when a filtered and very active solution of *fibrin* containing ten per cent. of sodium chloride is diluted with distilled water to seven or eight times its volume, a current of CO_2 passed through it causes the formation of a precipitate. "This precipitate," say these investigators, "treated directly *with tincture of guaiac becomes intensely blue.* Conversely, the liquid from which it was separated remains absolutely inactive." Now, Kühne, as Gamgee says, asserted that the precipitate thrown down by passing CO_2 through solutions of pure oxyhæmoglobin did not possess fibrinoplastic properties. He found also, according to Gamgee, that this precipitate "does not behave as a globulin" and that "it forms long, colorless fibers" resembling connective tissue. It seems plain that his precipitate was simply fibrin. As such it had obviously lost its fibrinoplastic properties and become *a compound of fibrinogen* and *oxidizing substance.*

All this shows that Schmidt was partly right when he concluded that the precipitate in question had fibrin-forming properties. But it proves, moreover: (1) that since fibrin is obtainable from blood drawn from any portion of the body, the oxidizing substance, which turns blue when treated to guaiac,

* The italics are Abelous and Biarnès's own.—S.
[133] M. Arthus: Jour. de physiol. et de path. gén., vol. iii, p. 897, 1901.
[134] Abelous and Biarnès: Arch. de Physiol., T. x, p. 665, 1898.

also circulates in all parts of the body, and (2) that since the adrenal secretion is a constituent of the oxidizing substance it circulates likewise in all tissues.

In the second place, there is no legitimate ground for doubt that, as I have already pointed out, it is the adrenal secretion *in the plasma* which carries on all respiratory processes.

When the secretion leaves the adrenals to reach the vena cava by way of the suprarenal veins, some of it at least must remain in the plasma. Thus Dreyer, whose experiments have been referred to, obtained effects similar to those evoked by adrenal extracts with blood derived from the suprarenal veins and which had been defibrinated and then filtered through muslin. Biedl used blood which had been both defibrinated and centrifugalized, and he specifies that it acted as effectually as the whole blood—a fact which led him to conclude that the "active substance" was "also contained in the serum." The experiments of Battelli referred to above were also performed with *serum*, and it was in this fluid that he found adrenalin. While Biedl used serum from the adrenal vein, Battelli analyzed serum from the general circulation—a fact which indicates widespread distribution of the secretion.

That it is a constituent of the plasma which appropriates the adrenal secretion is further shown by the fact that the proportion of blood-cells in the circulating blood does not influence the respiratory exchanges. Pembrey and Gurber[135] found that these remained the same in rabbits deprived by bleeding of one-half of their blood-corpuscles. As the liquid portion of the blood is restored at the expense of the lymph circulation, the proportion of red corpuscles was reduced one-half. Pettenkofer and Voit[136] have also shown that cases of simple anæmia, in which, therefore, the red corpuscles were greatly reduced in number, absorbed as much oxygen and excreted as much carbon dioxide as healthy men upon a similar diet and at rest. Suggestive in this connection is that this corresponds with Bohr and Henriques's previously mentioned observation that when all the arteries given off by the aorta were ligated, the respiratory exchanges were sometimes *increased*, and that it was only when

[135] Pembrey and Gurber: Jour. of Physiol., vol. xv, p. 449, 1894.
[136] Pettenkofer and Voit: Zeit. f. Biol., Bd. v, S. 319, 1869.

the inferior vena cava (the sole pathway for the adrenal secretion) was also obstructed that they dropped to a minimum. This plainly shows that it is the adrenal secretion which sustains the respiratory process.

Finally, it is evident that all this refers to the *free, i.e., albuminous* portion of the hæmoglobin, for we have already seen that when the guaiac test was applied to a solution in which the contents of the red cells, including the iron-laden hæmatin, had been voided, a muddy-red color appeared instead of the typical blue.

These three cardinal facts being established, the presence of the active principle of the adrenals in the blood-plasma of the entire organism asserts itself, since the *heat* and *solubility* tests correspond with the *color* test (the guaiac blue) at every stage of organic life, *i.e.*, from plant to man.

"We know," write Abelous and Biarnès,[137] "that *heat* enables us to separate two substances from sodium chloride and other neutral salt solutions of fibrin: one substance is precipitated between 56° and 58° C. and another is only precipitated *above* 70°." The nature of the first precipitate is well shown in the following sentence of Schäfer's,[138] concerning blood-coagulation: "A temperature of 56° C. prevents coagulation by precipitating the *fibrinogen* upon which the coagulation depends." Abelous and Biarnès refer to this body as "remaining inactive with guaiac," while the "fluid from which the precipitate had been separated markedly oxidized guaiaconic acid," *i.e.*, gave the blue reaction. "This experiment shows," add the authors, "that in saline macerations of fibrin, the *oxidizing agent* was not the globulin precipitating at 58°, but the globulin precipitating above 70°." What they mean by the latter is explained in the same paper by the statement that "the temperature of 100° C. causes organs [lungs, spleen, etc., and the fibrin] to lose the property of coloring blue the tincture of guaiac, while a temperature of 50° to 60° does not abolish this oxidizing property."

Now, wherever the oxidizing ferment has been referred to in its relations to temperature so far, we have seen that the

[137] Abelous and Biarnès: *Loc. cit.*, p. 667.
[138] Schäfer: "T. B. of Physiol.," vol. i, p. 146, 1898.

boiling point (100° C.) at least had to be reached before its activity was destroyed. This was found to be the case with the oxidizing substance of batrachians by Phisalix; of mollusks by Piéri and Portier; of crustaceans by Abelous and Biarnès, and of plants by Bertrand. The last named chemist, for instance, states that the plant ferment laccase "provokes direct oxidation of the bodies upon which it acts," but he also says that "with a boiled solution of laccase, or in the absence of oxygen [thus affirming its identity as a catalytic] it produces no coloration." We must not, however, lose sight of the fact that laccase is an *active principle*, and that it is this principle alone which can withstand temperatures at least up to the boiling point. The same principle doubtless exists in the mollusks studied by Piéri and Portier, since "50° and 60°C." and then 90° were applied in turn to the fluids tested, and their oxidizing activity only ceased when they had been boiled some minutes.

A similar resistance to the action of heat is shown by *adrenal extract*. Indeed, it was believed at first that even boiling could not destroy its physiological activity, but Moore[139] showed that it ceased to act when the boiling was continued for three or four hours. Even the adrenals *per se*, as observed by Cybulski, will no longer, after having been boiled, yield an active extract.

That the active principle of the blood's oxidase and that of the adrenals are identical is further demonstrated by the fact that their solubilities likewise correspond.

While Gamgee[140] states that hæmoglobin, which, as well as oxyhæmoglobin, exists "in colored blood-corpuscles in the form of loose or unstable combinations with some other constituent," is insoluble in absolute alcohol, chloroform, benzol, ether and other organic solvents, Vulpian[141] found that the expressed juice of the adrenals was also insoluble in organic solvents, alcohol, ether, benzene, etc., and that this applied to the extracts of *no other gland*. Gautier[142] also refers to the extract as being insoluble in alcohol, ether and chloroform. Gamgee includes carbon disulphide among these agents. Moore states

[139] Moore: Jour. of Physiol., vol. xvii, p. xiv, 1894-95.
[140] Gamgee: *Loc. cit.*, p. 206.
[141] Vulpian: C. r. de l'Acad. de sci. de Paris, Sept. 29, 1856.
[142] Gautier: "Chimie biologique," p. 355, 1892.

that the active principle of the adrenals is insoluble in ether, chloroform, amyl alcohol and carbon disulphide.

The constituent of hæmoglobin which can thus be precipitated from its solutions is evidently contained in its albuminous portion (94 per cent. of hæmoglobin, the remaining 6 per cent. being hæmatin), since it is also precipitated by alcohol as is laccase from its solutions, as stated by Bertrand, and from the extract of gills and palps of mollusks, which contain no coloring matter, as observed by Piéri and Portier. Alcohol precipitated the active substance from fibrin extract—free from hæmatin, of course—in solution, as stated by Abelous and Biarnès. Now, adrenalin, which, as pointed out by Battelli, is widespread throughout the plasma, is precipitated by the same reagents. Takamine, its discoverer, found that it was insoluble in alcohol, ether and chloroform.

Conversely, adrenal extracts were found very soluble in water, by Vulpian, and the hyaline droplets or granules of secretion derived from the adrenals likewise by Manasse.[143] Bertrand found the laccase of plants very soluble in water; the same property belonged to the oxidizing bodies in the crustaceans studied by Abelous and Biarnès. Finally, adrenalin, though very slightly soluble in cold water, is soluble in warm water, and readily so at the temperature of the blood-stream.

The correspondence between the chemical properties of adrenal extracts, adrenalin and other adrenal extractives with those of the active principles of the oxidizing substance or oxidases wherever found thus shows *that a ferment of which the active principle of the adrenal secretion is a type is the active agent in the oxygenation processes of all plants and animals.*

Concluding Remarks.—Pembrey,[144] in the recently published work already referred to, clearly defines the two antagonistic views as to the nature of the respiratory process as follows: (1) "The gaseous exchange between the blood and the alveolar air is due to the relative partial pressure of the gases in the blood and alveolar air, and can be explained according to physical and chemical laws;" (2) "the gaseous exchange takes place

[143] Manasse: *Loc. cit.*
[144] Pembrey: *Loc. cit.*, p. 543.

in opposition to the known physical and chemical laws, is of a special nature, a vital process akin to the secretion and excretion of glands." As interpreted from the evidence and conclusions submitted in the present work, the second view assumes another aspect:—we are not dealing with processes which in any way stand in opposition to known physical and chemical laws, but with processes in which the relative partial pressure of gases *does not enter at all.*

According to this interpretation, it is because the diffusion doctrine is a misapplication of the physical and chemical laws referred to that its sponsors even at this late date (1906) fail to agree. "So great is the want of agreement and irregularity of the results obtained by different observers with various forms of tonometer," writes Pembrey, an able and impartial reviewer, "that the suspicion arises that there are sources of fallacy in the methods." The chief of these, as I have pointed out, is reduction of the oxygen of the blood during its passage into and through the instrument. Indeed, when Bohr devised one "through which," says Pembrey, "a constant and rapid stream could be maintained," the results were such as to show that "the absorption of oxygen in these cases could not be explained by diffusion." Haldane and Lorrain Smith not only confirmed these results, but in their experiments, "the pressure of the gas in the *arterial blood* [was] *higher in every case.*" *

In the first volume, I pointed out that it was the secretion of the adrenals which took up the oxygen of the air to carry it to the tissues. We have seen in the present chapter that this conclusion was warranted. I may add that at every step of these researches an earnest effort was made to find evidence tending to weaken this conception and that not a single experimental fact was found which did not harmonize with it. That the diffusion doctrine has totally failed in this connection even among its defenders, we have seen. In comparison with this doctrine at least, therefore, the following conclusion stands proven:—

The physiological function of the internal secretion of the adrenals is loosely to combine with the oxygen of the air in the

* The italics are my own.—S.

pulmonary alveoli and to endow the blood with its oxygenizing properties.

ADRENOXIDASE.—As the term "oxyhæmoglobin" includes the hæmatin of the hæmoglobin molecule as well as its albuminous constituent (the oxidizing substance or oxygenized adrenal secretion), it cannot be used to denote the latter, which alone carries on all oxygenation processes. Nor is the term "oxidizing substance" applicable, since it refers to any agent capable of oxidizing. Hereafter, therefore, I will call this body "*adrenoxidase*," a term which embodies four salient features: its origin, the adrenals; its general distribution as suggested by "oxidase;" the identity of its active principle not only as a ferment, likewise suggested by "oxidase," but also as a catalytic, a property common to all oxidases.

CHAPTER XIV.

THE ADRENAL ACTIVE PRINCIPLE AS THE FERMENT OF FERMENTS.

ADRENOXIDASE AS A CONSTITUENT OF ENTEROKINASE AND OF TRYPSIN.

Notwithstanding the considerable work bestowed upon the pancreatic and other intestinal ferments, their nature has remained obscure. Moore,[1] for instance, writes: "Practically nothing is known of the enzymes of the small intestine save their action on foodstuffs, none of them have been obtained in even approximately pure condition, and the fact that they are enzymes rests on the observation (1) that the action is destroyed by boiling and (2) that it takes place under antiseptic conditions." As the oxidizing ferments alone resist heat up to the boiling point; and as Schoenbein[2] found oxidases in all secretions, the likelihood that the adrenoxidase plays an important part in intestinal digestion is very great, especially in view of the fact that all secretions obtain their fluids from the blood. This is further emphasized by the facts that the active principle of adrenoxidase is a catalytic, as we have seen, and that the ferments are known to possess this property. Thus, Moore, after defining the meaning of catalysis, states that "ferment actions are such catalytic reactions."

A zymogen or mother-substance, as is well known, is itself inactive. "The enzymes of the pancreatic secretion are derived from the granules in the cells," says Howell,[3] "but other facts show that the granules do not contain the enzymes as such, but a preparatory material or mother substance to which the name zymogen (enzyme-maker) has been given." Stewart,[4] moreover, states that the "fresh pancreas is devoid of trypsin," but that "it contains a substance which can readily be changed into trypsin; and this substance is soluble in glycerine, for the

[1] Moore: Schäfer's "T. B. of Physiol.," vol. i, p. 341, 1898.
[2] Schoenbein: Jour. f. prakt. Chemie, Bd. lxxxix, 1863.
[3] Howell: "Amer. T. B. of Physiol.," vol. i, second edition, p. 235, 1900.
[4] Stewart: "Manual of Physiol.," fourth edition, p. 324, 1900.