

ond third. It must be remembered that at times there may be great variations. An idea of the anatomic construction of the antrum can be obtained by noticing how the teeth grow and by taking note of the palatal arch. Now and then there is an almost complete septa between the antra so that one cavity might be entered and not the other. Dentists must be instructed concerning the nasal side of these cases, and they can instruct physicians as to the dental side. It does not seem to Dr. Richards that the dental route is the better. The patients who may be treated through the alveolar process may be treated better through the nose. An opening through the mouth is abnormal and the alveolar opening always tends to close. The patients treated through the mouth continue coming to the clinic for a long time. He does not think many American patients would care for such an operation. In his district most patients would prefer to have a little purulent discharge through the nose, rather than to have a so-called radical operation. In reply to a question, Dr. Richards stated that the radical internal method is not indicated in cases in which there is mucoid or polypoid degeneration, though it may give a certain amount of preliminary information. As a diagnostic measure the opening can be made through the nose. In acute cases, recovery usually follows the relief of pressure. In cases complicated with empyemata of the ethmoidal cells or of the frontal or of some of the other sinuses, he would make the opening under the inferior turbinate. If the patient seemed to have insufficient drainage, he would enlarge the opening. If the inferior turbinate lies in such a way that it folds right over the antral wall so that sufficient room cannot be obtained, part of it may be taken off. Again, the front end of the inferior turbinate can be taken off. The cases must be individualized. In a case with comparatively smooth walls and comparatively uncomplicated, drainage and washing will usually suffice. It does not matter so much how long these cases have lasted; more depends on the character of the pus and the condition of the mucous membrane. In cases with polypoid masses, it is better to operate through the canine fossa, unless the instruments presented by Dr. Myles will enable the operator to get sufficient drainage in these cases.

Dr. OTTO T. FREER, Chicago, said that he thinks that Dr. Richards has been a little unjust to the dental engine. The handpiece may be disinfected and he should not like to give up the use of so valuable an instrument merely because it can not be cleaned like the implements used for a laparotomy. Dr. Freer certainly has never seen sepsis follow his frequent use of the nasal burrs and trephines. The long burr cuts away the strong ridge left at the bottom between the nasal floor and floor of the antrum, after resection of the upper part of the nasal wall of the maxillary sinus, in a way no other implement can, so that the nasal floor shelves down into the antrum and drainage becomes as nearly perfect as possible. The trephine also perforates the nasal wall with great speed in several places and causes practically no pain. After the trephine the burr may be used to enlarge the opening.

## METHEMOGLOBIN AS A FACTOR OF CONSERVATIVE METABOLISM.\*

BERNARD OETTINGER, M.D.

Neurologist to the Hospital for the City and County of Denver.  
DENVER, COLO.

### DEFINITIONS.

Hemoglobin (Hb) is a crystallizable body which constitutes the largest portion of the colored corpuscle. It is a respiratory pigment, has the power to attract oxygen and also other gases. (Kirk.)

Hemoglobinemia is a condition in which the hemoglobin is dissolved out of the red corpuscle and is held in solution in the serum. (Gould.)

Oxyhemoglobin (O<sub>2</sub>Hb) results when hemoglobin is united molecule for molecule with oxygen. It is the char-

acteristic constituent of the red corpuscle to which the scarlet color of arterial blood is due. (Gould.)

Reduced hemoglobin is the result of deoxidation of oxyhemoglobin. (Gould.)

Methemoglobin (Met Hb) is a modified form of hemoglobin. It is the product either of incomplete decomposition of hemoglobin or of its excessive oxidation. The oxygen is more firmly combined in it than in oxyhemoglobin. (Gould.)

Methemoglobinemia is the presence of free methemoglobin in the blood. (Gould.)<sup>1</sup>

To the physician of to-day, methemoglobin, because it is known to be a more stable oxygen compound than oxyhemoglobin and is capable of reduction by the tissues only in slight degree, is universally regarded as a blood change deleterious to the organism, or, otherwise to express the equivalent, methemoglobinemia is always an intoxication, be it great or little in degree. It is amply proved that if methemoglobin be present in the blood in sufficient amount death results. Nevertheless, I differ from accepted opinion in so far as to say that methemoglobinemia must not be regarded as invariably deleterious to conservative metabolism, and that, in fact, therapy empirically makes use of this blood change to aid in conservation of nutrition. The following is offered in support of this opinion:

The toxicologist, Selmi, used the word ptomain to describe certain alkaloidal bodies formed during the process of animal tissue putrefaction. Herein the name derived from the Greek word signifying cadaver was appropriate enough. Gautier applied the name leucomain, from the Greek term signifying white of egg, to basic substances preformed in the body tissues or which are products of living tissue metabolism. This distinction, it was found, could not stand. Because putrefaction and normal digestion are practically identical processes, we are not surprised that some of the basic substances originally obtained from putrefying animal matter can be isolated from living protoplasm, both animal and vegetable. More than this, enzymes or unorganized ferments and dilute mineral acids are capable, as well as bacteria, of producing ptomains when acting on the nuclein molecule. These facts enable us to draw conclusions from findings in reference to such basic substances without regard to the usual dual classification. Concerning this argument, however, so much may be said as to their differentiation. The interdependent relation, as based on chemic formulæ, of some of these basic substances (leucomains) to others of the same class and their final elimination products, has been identified with successive oxidation and cleavage processes, as, for instance, those of the best known purin group, form a continuous oxidation series with uric acid as the final product from which urea may be attained by cleavage. Much less is known of antecedent and also of oxidized elimination forms of representative ptomains, such as cholin, muscarin, putrescin, etc., although, as a general proposition, the sufficient oxidation of these basic substances is known to render them innocuous. For the same reason, the relation in general between oxidation of metabolic products and pathologic reduction of red cells hereinafter considered, is clearer as regards the leucomains than the ptomains, although a like

1. This definition given because as complete as any attainable, nevertheless does not convey the entire meaning of the term methemoglobinemia as used in this article. In experimentation on animals it has been found that an induced blood change from oxyhemoglobin to methemoglobin, in most cases, if not always, takes place within an intact red cell, disintegration occurring later, and hence we obviously may have a methemoglobinemia before the methemoglobin becomes free and reaches the plasma.

\* Read in the Section on Pathology and Physiology of the American Medical Association, at the Fifty-sixth Annual Session, July, 1905.

need for the oxidation of the latter remains no less obvious.

As clinicians, we are interested in the connection which retention of these basic substances may have to disease—a factor often recognized, at least, in general terms. C. E. Simon<sup>1</sup> says “both classes of substances (i. e., ptomains and leucomains) are of especial interest to the physician, as their formation or undue accumulation in the body may give rise to serious disturbances.” Vaughan and Novy<sup>2</sup> state “the leucomains have been credited by many as playing the chief rôle in auto-intoxication,” and, again, “Wiener’s observations on uric acid show that the purin body is not only a nuclein cleavage product, but that it may also be a synthetic one. Furthermore, he has shown that uric acid is not only being made, but is also being constantly destroyed within the body.”<sup>3</sup> The process of formation and decomposition results in the normal minimum excretion of uric acid. If, however, the latter change be diminished or inhibited, the amount of uric acid becomes apparently increased and may lead to disease conditions, such as rheumatism. The same view may be extended to the purin bases and the relatively large elimination of these bodies in leukemia may be due not only to increased formation, but also to decreased destruction.”

As regards specific blood observations, Prevost and Dumas have noted an accumulation of urea in the blood where it failed of elimination by the kidneys,<sup>4</sup> and, according to Gschleiden, an accumulation likewise occurs in fever. Salomon found uric acid in the blood in demonstrable amounts in cases of pneumonia and fever. von Jaksch obtained blood by cupping from 102 persons, of which only a few were in health, and tested it for uric acid. He detected no uric acid in the blood of the healthy, but found it in varying amounts in the blood of patients who, as a result of heart lesions, of pneumonia, nephritis or anemia, were suffering from dyspnea. The same investigator detected xanthin bases and uric acid in exudates and transudates and also the former in the blood in various pathologic conditions. According to von Limbeck,<sup>5</sup> xanthin bases (i. e., purin bases) have been found in the blood in various diseases by Sherer, Mosler, Salkowski and Salomon. von Jaksch interpreted the accumulation of uric acid in the blood in dyspneic conditions to mean that in these occurred greatly lessened oxidation processes. von Limbeck points out that the error of this conclusion is demonstrated by Kraus, who, by comparative analyses of respired gases in cases of severe anemia as against those of healthy persons, found the coefficient,  $\frac{\text{CO}_2}{\text{O}_2}$ , to be the same in both conditions. In accordance, also, are the observations by Chrostek, Bohland and Biernacki that in simple anemia the patient, instead of using less oxygen, employs rather more than in health. A reasonable conception concerning all blood conditions which have been cited would be the following one, viz., that as a pathologic effect in a great many morbid conditions increased disintegration of tissue cells results in the increased formation of leucomains, the chief known source of which are the nucleins of the nuclei and the proteids of

cell protoplasm. Also, it being established that progressive oxidation and subsequent cleavage advances the leucomains to a product suitable for body elimination or one required for further metabolism, *dyspneic conditions (without regard to clinical entity but merely as one sign of intoxication), are always manifestation of an inadequate effort on the part of the organism sufficiently to oxidize these cell disintegration products.* Or, to express the idea from a different view-point, *there is in the blood in conditions which result in increased tissue metabolism an accumulation of basic products which are prepared for further use or for body elimination by oxidation and cleavage processes, and, therefore, the same products up to the point of their sufficient preparation act as powerful reducing agents or deoxidizers.*

To one who approaches the subject without prejudice, the literature of methemoglobinemia develops some unconvincing conclusions as well as patent contradictions. He must be impressed by the fact that substances so far removed from others classed with them in physiologic effect or manner of therapeutic use as are hydrocyanic acid, amyl nitrite, iodine, turpentine, pyridine, chloroform, ether, chlorate and permanganate of potash, phenacetin and other antipyretic coal-tar products, certain toadstool and snake poisons, etc., require differentiation in the consideration of a systemic effect, even though all of these possess a common property to produce in sufficient dose a certain toxemia. He notes the statement by one investigator that before certain substances can change oxyhemoglobin to methemoglobin the hemoglobin must be freed from the corpuscle by the latter’s disintegration. Another observer is equally certain that even in these cases the change to methemoglobin is primary and that the solution of the red cell occurs subsequently. If, as in this case, the same substances, as, for instance, arsenuretted hydrogen, snake venoms, toadstool toxins, be set down by a third authority as producers of hemoglobinemia only, the suspicion is born that at the door of the met compound, perhaps, are laid some of the ill effects of poisons whose paramount action is rapid solution of the red cells. It is true that disintegration of the red cell does follow methemoglobin formation,<sup>6</sup> and it is not surprising, for the reason that

6. The following are summaries of two detailed studies of fatal methemoglobinemia: Brandenburg’s case, a woman 28 years old, who drank at night a solution of 525 grains of potassium chlorate in water was received at the clinic the following morning. The blood examination showed severe leucocytosis, polkilocytosis, but these not numerous; also irregularly shaped large and small red cells. The blood was chocolate brown, and showed by spectroscopic examination, the bands of methemoglobin. The separated serum had a brownish tinge, contained methemoglobin, as did also the urine. Counts of red cells from the first to the seventh day demonstrated a daily decrease in red corpuscles as follows: 4.3 mill., 2.5 mill., 2.3 mill., 2.1 mill., 1.9 mill., 1.6 mill. After the fifth day no methemoglobin could be found in the serum. Necropsy following on the seventh day, exhibited parenchymatous inflammation of the myocardium, the liver, stomach mucous membrane and kidneys, the last also showing intense hemoglobin infarcts. (Grawitz.)

K. Ehrlich and Lindenthal’s Case.—Ten hours after initial symptoms of poisoning by nitrobenzol, the blood was chocolate colored, the serum brownish. The spectral analysis showed presence of methemoglobin, which disappeared on the eighth day. Red cells were rapidly reduced, 2,275,000 on the fifth day, and falling to 900,000 before death on the nineteenth day. Polkilocytosis appeared on the third day and soon reached a remarkable degree. Polychromatic and fragmented cells were abundant. Nucleated red cells were first seen on the third day, and thereafter in very large numbers of all sizes. On the ninth day, the leucocytosis previously low, rose suddenly to 61,000, and the nucleated cells reported at 24,700. The Hb fell steadily to 40 per cent., which, with 900,000 cells was a remarkably high Hb index. There were many myelocytes among the white cells, so that at one time the blood presented the appearance of leukemia. (Ewing.)

Mohr observed six cases of benzol poisoning among workers in benzol factories. In all there was methemoglobinemia, schistocytosis and hemoglobinic degeneration, while nucleated red cells, microcytes and macrocytes were numerous. (Ewing.)

1. Simon, Chas. E.: Text-Book Physiological Chemistry, 1904.

2. Vaughan and Novy: Cellular Toxins, 1902.

3. In this case, although successive oxidation is not followed by elimination, it nevertheless has played an equally important rôle in the antecedent metabolism.

4. Baginsky holds that the amount of the purin base, xanthin normally present in the urine may be increased tenfold in acute nephritis.

5. Limbeck, Rud. R. von., Grundriss einer Klinischen Path. des Blutes, 1896.

this superoxidation<sup>7</sup> of the corpuscle is needless in health and hence always presents an extraordinary form of hemoglobin. Yet, a legitimate question may be raised whether or not some other agent, beside that which produces the met oxidation, may not sometimes complicate the latter effect—for instance, the albumin destroying property and, therefore, destructive effect, on the red cell of potassium in the oft quoted met toxemia of potassium chlorate—a result which was manifest in experiments on herbivorous animals (rabbits); or, again, the possibility that in severe methemoglobinemia, the tissues being deprived of enough easily reduced oxyhemoglobin and unable to utilize the methemoglobin, do now attack the reduced hemoglobin, which, as we know, still contains considerable oxygen, deoxidizing it and, in turn, its derivatives up to corpuscular dissolution.<sup>8</sup>

Experimental research as to methemoglobin poisoning has been largely confined to the effects of potassium chlorate, because of the overwhelming blood change which follows the ingestion of large doses of this drug and the former comparative frequency of methemoglobinemia from this cause on account of common administration of toxic doses. A brief review of such research as given in von Limbeck's work on clinical pathology of the blood is as follows:

Marchand, who first experimentally studied the toxic effect on dogs of chlorin salts, stated that the absorption of the latter resulted in a methemoglobinemia which was the cause of death in acute toxemia. Against this conclusion, Stokvis took the position, from experiments chiefly on rabbits, that death in chlorate poisoning was solely due to salt effect and that the formation of MetHb was a postmortem change. This view was apparently refuted by Lenhart and Riess, who demonstrated methemoglobin in intravascular blood of the animal experimented on. Following these experiments, von Limbeck was able to show by volumetric computation of O in the blood of dogs poisoned by NaClO<sub>3</sub> that in the latter, and possibly also in man, death in acute chlorate poisoning is due to asphyxia, resulting from lack of reducible hemoglobin. How great, says this observer, is the toxic effect of the chlorate salt as such on the organism, remains an open question which, while it can not be eliminated, may be answered in so far that for dogs and in acute poisoning, this effect is probably subsidiary to asphyxia as a cause of death. For herbivora this conclusion does not hold good. Stokvis, Marchand and Bokai showed that, with rabbits, death followed acute chlorate poisoning in almost all cases without the characteristic blood change and that at least a period of one and a half hours after death needed to elapse before methemoglobin could be demonstrated in the blood. Here the cause of death could be ascribed to the effects of chlorate salts as such. There was no disintegration of corpuscles nor did this seem to occur in acute poisoning of dogs. According to von Limbeck, in subacute methemoglobin poisoning, one must reckon with a greater number of complicating conditions which include production of methemoglobin, effect of salt as

such on the tissues, decomposition of blood corpuscles, circulatory disturbances due to thrombi and, as the factor of chief importance, kidney irritation.

As subacute toxemia is the only form that would have to do with this argument, we are especially interested in its several dangers—certainly each as a toxic effect is sufficiently evil. And yet, aside from mere production of methemoglobin, which needs a 66.6 per cent. blood change to be fatal, if the physician as he prescribes, could not depend on his judgment to guard his patient from grave tissue change arising from injudicious treatment as regards dosage and period of drug administration, said treatment causing, for instance, great cellular disintegration of the kidney, the liver or other excreting organs, he would need to take from his drug armamentarium many important constituents of it, such as chloral, phosphorus and its compounds, bromin salts, the coal-tar antipyretics, salicylic acid and its derivatives, etc. Hence, if it then be a matter for the physician, not that he must ever avoid a methemoglobinemia as such, but that in therapeutic use of substances capable of producing this blood change, he must avoid a toxemia in his patient, we find herein quite the same problem to solve in relation to these drugs as confronts us in the use of most others we employ in treatment. And, in the same case, the practitioner must be accorded the right to produce a methemoglobinemia of non-toxic proportions if he can benefit the patient thereby.<sup>9</sup> I believe the patient may be, and indeed is, often benefitted by an induced methemoglobinemia effected by drugs now empirically employed, *by oxidizing through this means the suboxidized leucomains which we have found in time of disease, accumulate in abnormal amounts in the blood. These powerful reducing agents are able to take O from methemoglobin, although the tissues can not.*<sup>10</sup> In the asphyxia of extensive and, therefore, toxic methemoglobinemia, pulmonary respiration is, to a great extent, eliminated, because the hemoglobin, unreduced by the tissues, is brought to the lungs already oxygen laden. Herein methemoglobin acts as no special poison, for oxyhemoglobin returned to the lungs would give them as little to do. On the other hand, the partial asphyxia of disease, as evidenced by dyspnea and cyanosis, has as one, if not exclusive cause, *the increased amount of oxygen required by the system to oxidize the tissues plus the leucomains or other like basic reducing substances, with which need the lungs can not keep pace.*

*With an induced methemoglobinemia in just that degree that may be required to sufficiently oxidize the basic substances, thereby preparing them for elimination or for further use in the animal economy, we obtain two paramount results: (1) The O<sub>2</sub>Hb is conserved for use of the tissues.* In reference to this statement, it is true that methemoglobin contains the same number of oxygen atoms as oxyhemoglobin, which point might be advanced as an argument that the leucomains could as well be oxidized by the normal oxy-compound as the

7. "In apparent contradiction to the fact that bacteria are capable of converting MetHb. to Hb. is that demonstrated by J. F. Lipowski that by means of pure cultures of other bacteria O<sub>2</sub>Hb can be changed to MetHb. In the first case we have to do with reducing, in the second with oxidizing and oxygen-forming microbes." (Rudolf Kobert.)

8. If CO<sub>2</sub> be passed through a solution of oxyhemoglobin for a considerable time, reduced Hb is first formed, but if the process be prolonged, the Hb is decomposed, a precipitate of globulin is thrown down and an absorption band similar to that obtained when Hb is decomposed with acids (acid hematin) is observed. (Landois and Sterling.)

9. But for a generation of prejudice, originating in the therapeutic abuse of potassium chlorate and which pronounces all methemoglobinemia essentially toxic, a conclusion so self-evident would scarcely need discussion, if we but remember our daily use of three of the MetHb producing halogens in the form of iodine, chlorine and bromine compounds or salts, also the coal-tar analgesics and antipyretics. That one is called on to exercise care as to dose and period of administration of this class of drugs so as to avoid pushing a methemoglobinemia beyond therapeutic limits or because of other possible deleterious effects there is no question.

10. "It (methemoglobin) is, however, affected by the products formed in the blood during asphyxia, while COHb is not, the MetHb formed by the nitrites is reduced by these products to Hb, which as it passes through the lungs takes up O." (Landois and Sterling, Human Physiology, Fourth Edition, 1892.)

met-compound. It must be remembered, however, that the oxygen of the latter is in a different form wherein the oxygen atoms are more closely bound within the molecule than in oxyhemoglobin, and therefore the met molecule requires in all probability a greater amount of suboxidized basic material for its reduction than would be needed for the loosely bound normal oxy-compound.<sup>11</sup>

(2) *Some oxyhemoglobin is produced within the tissues, and herein vicarious function for an embarrassed pulmonary respiration is established.* The view that oxyhemoglobin may be furnished the organism otherwise than by the lungs may appear radical, yet apparently forces acceptance in the light of the following observations, viz., that if a careful decomposition of methemoglobin be made in glass by just enough of the reducing agent to permit the process to proceed slowly, spectroscopic examination will demonstrate the presence of oxyhemoglobin absorption lines before those of reduced hemoglobin are attained, the sequence, therefore, being methemoglobin, oxyhemoglobin, reduced hemoglobin (Jaderholm). Not only this, but the reverse is also true. If reduced hemoglobin be slowly oxidized to methemoglobin in glass, the spectroscope shows that here, too, oxyhemoglobin is an intermediate compound, the sequence being reduced hemoglobin, oxyhemoglobin, methemoglobin (Saarbruch). The similarity of chemical reaction that attends methemoglobin formation and its reduction in the experimental animal to the same procedure without the body permits us to believe that where either of the preceding reactions occur during life oxyhemoglobin must also appear as an intermediate product. Hence, in induced, slight methemoglobinemia some of the methemoglobin reduced to oxyhemoglobin by leucomains is, no doubt, further reduced by the tissues themselves, or, again, in the course of an induced oxidation from reduced hemoglobin to methemoglobin not all of the intermediate oxyhemoglobin would attain the methemoglobin state, because of the appropriation here also of some of the former by the tissues. This conception of methemoglobin utilization in disease. it will be noted, differs materially from earlier theory that the internal administration of potassium chlorate benefits by furnishing oxygen to the tissues in the course of its decomposition. The present hypothesis includes a series of reactions, (1) superoxidation of reduced hemoglobin or oxyhemoglobin to methemoglobin; (2) reduction of methemoglobin to reduced hemoglobin, with concurrent oxidation of reducing substances in the blood; (3) the occurrence of oxyhemoglobin as an intermediate product in course of corpuscular oxidation and reduction.

But, it may be urged, if methemoglobinemia at any time be other than harmful, how comes it to be associated with various pathologic conditions and in these without extraneous origin? It has been found in exudates and transudates, also in the blood following severe burns and scalds, in insolation, septic conditions, in Addison's disease, etc. The question may be answered thus: In these and probably many other morbid conditions, methemoglobinemia (always noted as only

a trace and by no means of a degree that could be responsible for death of the patient) represents a conserving process of nature which we imitate by inducing therapeutically a like blood change. Nature accomplishes this by the products of metabolism. Of such products, which produce methemoglobinemia, two which may be cited are pyrocatechin and hydrochinon, and doubtless there are many others.

Viewed from the dual standpoint of oxidizer, both of reducing substances in the blood and of the tissues themselves when for some reason pulmonary respiration is inadequate to furnish sufficient oxygen, induced conservative methemoglobinemia would explain the present empiric use of substances which produce the met compound, viz., nitrite of amyl in angina pectoris, pyridin inhalations in asthmatic attacks, potassium chlorate in tonsillitis and its occasional use, long continued and with success to prevent recurrent abortions, the bromin salts in epilepsy, iron as the perchlorid in chorea minor and as insisted on by the older practitioners in sepsis, Lugol's solution and the iodid of iron in scrofulous and cachectic conditions, potassium permanganate in anemia, quinic acid<sup>12</sup> recently recommended as specific treatment in gout, etc.

Because fumes of pyridin proved useful in asthmatic attacks, I concluded to try potassium chlorate as a constitutional in the same condition, and obtained good results, although I would not care to have a patient continue long on this drug, or at least without constant supervision, for fear of damage to the kidneys. Also, one need be clear as to one point. I do not mean to say that, because each of a number of drugs can produce a methemoglobinemia, they may be indifferently substituted in treatment, one for another. Without doubt other affinities, too, of these remedies must decide our choice. The rapid but evanescent relief from dyspnea and vasomotor spasm effected by use of amyl nitrite or pyridin fumes could not well take the place of the prolonged effect on metabolism of potassium chlorate or the latter of the bromin salts which experience has shown approaches specific effect in epilepsy. Yet substitution of met-producing drugs is, to some extent, efficient, as we have seen, and may again be noted herein that the one vegetable drug which it has been found fills a serviceable place beside the bromids in the treatment of epilepsy is *Solanum carolinense*, a plant which belongs to one of several classes that contain so-called saponin bodies, glucoside substances which produce methemoglobin.

There are many other facts pertinent to this line of thought which might be added, but enough has been said if, in response to this first paper, members of the profession, and especially such observers as are able concurrently to utilize clinic and laboratory, will find the subject of sufficient interest to test the principle here advanced, full confirmation of which would materially extend the province of rational therapeutics.

I take pleasure in expressing my obligation to Prof. W. E. Engle of the University of Denver for the privilege of working in his laboratory and for his assistance in examination of blood with the spectroscope.

Since writing the above article J. von Mehring's<sup>13</sup> frequently quoted thesis on potassium chlorate has come into my hands. One important conclusion of von Mehr-

11. In reference to this, the fact already pointed out, that methemoglobinization of the red cell is equivalent to a superoxidation, is again of interest here, in that it suggests the possibility that the O atoms when freed act as nascent O. According to Engler's views, the first step in systemic oxidation is the decomposition of peroxids by that class of ferments, known as peroxydases, while, according to Landols and Sterling, it is the active or nascent O that acts as so powerful an oxidizing agent that it converts water into hydic peroxid, N of the air into nitrous and nitric acid and CO into CO<sub>2</sub>, which ozone does not.

12. Dry distillation of quinic acid yields pyrocatechin and hydrochinon (U. S. Dispensatory 17 Ed., page 1432) both of which transform O<sub>2</sub>Hb to MetHb.

13. Mehring, J. von: Das Chlorsaure Kali, 1885.

ing was "that with an accumulation of  $\text{CO}_2$  in the blood (blood from carotid artery in dyspnea) and in an amount not resulting in death, the deleterious effects of  $\text{KClO}_3$  are increased in great degree" (i. e., absorption bands of methemoglobin were noted after a much shorter space of time than with normal blood from the carotid). The same result was observed after addition of small amounts of acid sodium phosphate to blood.

My own conclusions are just contrary to the above where slight, therapeutic methemoglobinemia is concerned, and which may, therefore, be stated thus—in dyspneic conditions, the greater the rapidity of an induced methemoglobinemia proportionate to the needed oxidation of increased amounts of reducing substances in the blood, the greater and more rapid the benefit to the patient. This is also in accord with personal clinical experience as regards relief of dyspnea by administration of certain methemoglobin-producing drugs in small amounts. I have not tested the effect of this same class of drugs in phosphorus poisoning, but I find in von Mehring's thesis the following reference: "Tessliers<sup>14</sup> observed at the clinic of du Moulin in Ghent a case of phosphorus poisoning, wherein the patient, owing to great repugnance to turpentine, was given potassium chlorate, with apparent beneficial results." It is significant that turpentine shares with potassium chlorate methemoglobin producing properties.<sup>15</sup>

## SYMPTOMS, DIAGNOSIS AND PROGNOSIS OF UNCOMPLICATED INTESTINAL AMEBIASIS IN THE TROPICS.

W. E. MUSGRAVE, M.D.

Pathologist, Government Laboratory; Physician in Chief,  
St. Paul's Hospital.  
MANILA, P. I.

### SYMPTOMATOLOGY.

The symptomatology of amebiasis varies more than is generally taught and it seems desirable that this more comprehensive clinical picture be taken up more in detail, calling particular attention to the early diagnosis of the disease and to some of the peculiarities of the milder forms.

In discussing this question, writers have generally divided the cases into groups according to the clinical manifestation which, as clinical conveniences, answer the purpose and are fairly uniform. Osler considers it under the headings acute and chronic. Harris divided the disease into very mild forms, moderately severe cases and very severe ones. Lafleur and Fletcher divide them into grave and gangrenous forms, those of moderate intensity and chronic ones.

I shall discuss the subject under the following conventional clinical divisions:

1. Latent and masked infections.
2. Mild and moderately severe ones.
3. Severe cases, including gangrenous and diphtheritic ones.
4. Infection in children and in the aged.

14. Annal de la Soc. de med. de Gand, 1882.

15. Other authorities which may be referred to are: Beilstein, F., *Organische Chemie*, Dritte Auflage. DaCosta, John C., Jr., *Clinical Hematology*, 1901. Ewing, James: *Clinical Pathology of the Blood*, 1903. Grawitz, Ernst: *Klinische Pathologie des Blutes*, 1896. Kobert, Rudolf: *Lehrbuch der Intoxicationen*, 2 vol., 1902-1904; U. S. Dispensatory, 17th edition, Article on Ptomaines, 1898. Wood, H. C., *Therapeutics, Principles and Practice*, 10th edition, 1897. \* Read in the Section on Practice of Medicine of the American Medical Association, at the Fifty-sixth Annual Session, July, 1905.

NOTE.—The other papers in this symposium will appear in a later issue of THE JOURNAL.

These clinical forms often change from one to the other and may do so several times during the course of the disease in the same patient. The amebic process in all is essentially chronic, but acute symptoms from concurrent or secondary infection by other agents are frequently seen.

*Latent Infections.*—By this term are designated those cases in which there is a true pathologic process, containing amebas without diarrhea or other symptoms which would ordinarily indicate the presence of such an infection.<sup>1</sup>

It might be objected that this latency is really a period of incubation. In a sense, this may be true, but as many of the cases, even fatal ones, always remain in this class, and as there are nearly always certain manifestations in addition to the positive one of the presence of amebas, it seems better to give latency a separate place in the clinical classification; and, furthermore, the most useful results will be secured by making such divisions rather sharp and by confining the incubation period in all classes of the disease to the unknown time between the infection and the appearance of amebas in the stools.

Under these circumstances it is readily seen how difficult latency may be to differentiate from what properly may be termed incubation. This becomes all the more difficult when we remember that amebas may possibly be found transiently in the normal intestine and that there are at present no practical means of differentiating between species of amebas. It is clear, therefore, that by basing treatment on the method of diagnosis recommended, unnecessary therapeutics may occasionally be instituted.

Cases of this latent class are not infrequent in Manila and are becoming more and more recognized, as we learn more of the character of the infection, and I do not believe that giving them a place in a purely clinical classification can be criticized by those who have had experience with the disease in the tropics. They are certainly of very great importance and deserve the most careful consideration, for the life of the patient often depends as much on the diagnosis and treatment here as it does in some of those clinically more active infections. Some of these patients, as has been noted, never show clinical manifestations during life, and in some others, when such symptoms do develop, the time for successful therapeutics may have passed.

The course and outcome, as in some other types, varies greatly. Usually, after a period ranging from a few weeks to many months, more active symptoms develop and in general the patient assumes the clinical type of a more or less severe dysentery. This change may occur gradually or very suddenly, and in the latter instance, unless the patient has been under very close observation, we may be misled into believing it to be one of primary acute amebic dysentery. On the other hand, some of these cases go on to recovery or death, without ever showing active diarrhea.

The symptoms during latency may be entirely absent subjectively and objectively for considerable periods of time; but usually conditions develop, which, by the aid

1. Dock, in 1891, reported extensive amebic ulceration in the cecum of a man who had not had dysentery and who had passed only normal stools. Councilman and Lafleur, in 1892, and Lafleur, in 1897, called attention to the fact that an amebic process may be latent, the stools being well formed and no amebas being found in the small adherent flakes of mucus, and that in these cases the true nature of the disease is often not suspected until abscess of the liver calls attention to it. These observations have been confirmed by Osler, Rogers and many other writers.