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On the Mode of Action of the Group of Vegetable bitters including Strychnia.

The unquestionably good results which, in certain circumstances, follow the administration of bitter alkaloids, presses home to us the question. How do these remedies act? There is no better established fact in the whole range of therapeutics than the good effect of Quinine in atonic conditions of the system and in intermittent fevers. Scepticism as to the use of drugs is very prevalent yet no one, we think, will doubt that Quinine frequently improves the appetite, gives tone to flabby muscles and shortens an attack of ague. Experience forces upon us the conviction of these truths, but as long as these truths are merely empirical, so long are they but half-truths. If we can hold a theory which, though imperfect, is in accord with the well ascertained facts of the subject we shall have gained something.

The group of drugs whose action we are about to consider comprises by common consent the vegetable bitter principles Quinine, Cinchonine, Quinidine, Salicine, Caffeine, Beberine &c & the bitter principles contained in Quassia, Calumba, Gentian &c. We shall, however, endeavour to show that Strychnine also should be included, and is by no means an unimportant member of the group. In what follows then we have two aims in view 1st To put forward some evidence in favour of a theory as to the mode of action of bitter tonics. and 2nd to show that Strychnine should be systematically included in this group of remedies.

We shall treat of these subjects in the inverse order in which we have here stated them.

We are aware that Strychnine is very generally used by the professcion as a tonic remedy, yet writers are slow to systematically classify it with Quinine

and other bitters. It is generally called a spinal stimulant, and only hesitatingly if at all placed among tonics or anto-periodics. In poisonous and in large medicinal doses it certainly is a stimulant of the motor roots of the spinal nerves, but in ordinary medicinal doses (say 1/30 of a grain) it is no more a stimulant than, and as much a tonic as Quinine. It is within the experience of most that the effects of Strychnine, given for some time in such doses as 1/30 of a grain, are not immediate or transient, (the mark of a stimulant); they are gradually produced and are more or less permanent like those of any other tonic. A somewhat large dose of Strychnine we have found to increase the rapidity of the pulse by a few beats in the minute, but Quinine the typical member of the group in question has, by careful observation, been found in large doses to have the same effect. (Ringer page 516)

A dose of about 3 grains of Ext. Nuc. Vom. caused in our own person a sense of fulness in the head, a warm flow over the whole surface of the body and a considerable loss of control over voluntary movement on making an attempt to walk. These symptoms are no doubt those of incipient poisoning, but the toxic effects of large doses of quinine, fulness in the head, ringing in the ears &c are quite analogous to them. An adverse opinion is that of Dr Headland who says (action of Medicines 4th ed page 146) "the results of large "doses of quinine in producing determination "of blood to the head, ringing in the ears and "vomiting seem to me to mark its action "as an <u>irritant</u> poison, and not to be "characteristic of tonic medicines. For all "medicines except only the most powerful "sedatives act as irritants of the stomach "and intestines when given in an overdose".

For us it seems hard to see how an irritant of the stomach & bowels

could cause not only very intense headache and ringing in the ears, but also temporary blindness & temporary and even permanent deafness, all of which have been caused by Quinine. We consider these symptoms to be due to a poison absorbed into the system, and to be quite as specific in their character as Strychnine twitchings. Why Quinine chooses one part of the nervous system and Strychnine another is of course inexplicable.

It may be said that Quinine though producing disagreeable symptoms is incapable of causing death, and that consequently it should not be grouped with so powerful a poison as Strychnine. In reply we say that it is well known that Quinine destroys low forms of animal life, and that there is on record at least one case of death of a human being by Quinine. Recamier at the Hôtel Dieu gave a patient 46 grs of Quinine

one day and 53 prs the following day with the result of causing violent agitation, furious delirium & death (Farre's Pereira's Mat Med page 358). Quinine then is a poison, though a much weaker one than Strychnine, but its earlier toxic effects are so disagreeable as to prove a safeguard against a fatal dose being readily taken.

We believe it to be unnecessary to give particulars of cases in which we have found Strychnine to be useful as a tonic. It is sufficient to say that in debility with flabby muscles, in debility after acute disease, in indigestion with flatulence, heartburn & constipation, in cases of seminal emissions in subinvolution of the uterus after pregnancy and in other cases where there was need of a powerful tonic to act on the muscular system voluntary or involuntary we believe we have found Strychnine to give results which we would not expect to be surpassed by those of any other drug.

Again the similarity of the Chemical

formulae for Quinine & Strychnine is striking. They are

Quinine $C_{20} H_{24} N_2 O_2$ (Roscoe)

Strychnine $C_{21} H_{22} N_2 O_2$ (Roscoe)

Seeing that Strychnine resembles Quinine so much in other respects, we should naturally expect that it would prove useful in periodic diseases. It is to us a matter of surprise that it has been so much ignored in the treatment of Ague as it has been. The risk of giving an overdose is no doubt a deterrent. There are however two letters in recent numbers of the Lancet which are strong evidence in favour of its usefulness both as a prophylactic and as a curative agent in intermittents. In the Lancet for 3rd Nov 1877 Mr Waylen formerly Surgeon to the East Indian Railway Coy. writes. "Strychnine as a prophylactic "and curative agent in malarial fevers "has not hitherto to my knowledge received "the recognition that its merits demand

---------- "Having conclusively proved
"the curative powers of Strychnine in
"many long standing cases of Periodic
"fever, where the recognised specific, Quinine
"had failed in its beneficial effects whilst
"producing all the constitutional disturbances
"incidental to its exhibition, I was induced
"to employ Strychnine as a prophylactic,
"and the results exceeded my most sanguine
"expectations. My practice was to give 1/32
"of a grain of Strychnine combined with 1/4
"of a grain of Opium the first thing every
"morning, and among those who persevered
"with this precaution the cases of fever
"were very few and very mild in character"
This he says is written "after many years
"experience in the most notoriously unhealthy
"districts of Bengal & the North West Provinces
"of India" and we think it should have
weight accordingly. A fortnight later
in the Lancet for 17th Nov. Dr. G. De. G. Griffiths
formerly Med Officer to the P & O. Co. India
and China corroborates the above

and says that for years back he has used Strychnine for fevers instead of Quinine. After this we think there is some reason for making Strychnine rank along with the other Tonic and Antiperiodic bitter principles.

We now come to consider the mode of action of this Group of remedies. How is it that bitter principles improve the appetite, aid digestion, harden muscles and improve the general health & nutrition, and how do they reduce fever and shorten an attack of ague? Is there any theory tenable on rational grounds? It is generally allowed that the improved appetite & digestion are in part at least due to the topical action of the medicine. Its presence in the stomach corrects morbid conditions of the mucous membrane, and thereby promotes assimilation. But how does the presence of the bitter bring about the improved condition of the mucous membrane of the Stomach?

Stomachal digestion is allowed to be akin to fermentation, and pepsin is said to be analogous to the ferment. We think that if ~~fermentation~~ stomachal digestion is to be called a fermentation at all, it is nearer the truth to say that the active epithelial cells in the glands of the mucous membrane of the stomach are the ferment. This at least accords more with our idea of what a ferment is, as will be seen later on. The improved digestion following the administration of Quinine will be acknowledged by most to be due in part, at least, to the checking of over-digestion or over-fermentation in the stomach. Now this antifermentive or antiseptic power (for, as will be seen presently the meaning we attach to the two words is the same) of the drug, is, according to the theory to be advanced, the Key to the "modus operandi" both topical & general of the whole group of medicines that we have under consideration.

all the members of this group of drugs are tonic and antiperiodic; now we shall adduce what evidence we can in support of the view that their tonic and antiperiodic powers are due to their being antiseptics.

When we bring forward this theory we are at a loss to know whether it is being advanced for the first time. We cannot find it anywhere definitely stated in precise language, yet it would seem that Quinine especially has been tried in many diseases apparently at the promptings of a belief in this theory.

Outside of the body Quinine and its congeners are Antiseptic or Antifermentive (Ringer p. 573). In order to have evidence of this for ourselves we performed the following experiment, the results of which, though rather equivocal, had perhaps better be given. On 1st Dec. we set agoing eight test-tubes with contents as represented beneath.

These contents began to putrefy on the dates at the ends of the lines. By 'Ext. Carnis' we mean Liebig's Ext Carnis as sold in Shops. By 'Liq. Strychniae minus Strychnia' we mean water with the same proportion of spirit & acid, ~~which~~ as is contained in the Liq Strychniae B.P. but without any of the alkaloid.

			Gave way on
I	Ext-Carnis grs 2½	Aq. ad ℥iv	4th Dec
II	" " " 2½ + ℥j Liq Strychnae – Strychnia)	" " ℥iv	16th "
III	" " " 2½ + ℥j Liq Strychniae	" " ℥iv	27th "
IV	" " " 2½ + m15 " "	" " ℥iv	6th "
V	" " " 2½ + m8 Acid Nit Dil	" " ℥iv	30th "
VI	" " " 2½ + m8 Acid Nit Dil + grs 8 Quiniae	" " ℥iv	27th "
VII	" " " 2½ + m4 " " " + grs 4 "	" " ℥iv	14th "
VIII	" " " 2½ + m2 " " " + grs 2 "	" " ℥iv	7th "

Unfortunately about one third of the contents of tube V got lost some days after the experiment was begun, and in consequence of this, the surface of the fluid being much further away from the top of the tube than was the case

in the others, the chances of organisms getting in were considerably reduced. This is probably the explanation of No V holding out beyond No VI and all the others. In other respects the order in which the tubes gave way is much as we expected it to be, and, to some extent, it shows the antiseptic nature of the alkaloids. It is perhaps worthy of remark that the tubes containing Strychnia had the same kind of organism as No I had, while those with Quinine had another species of organism. The mishap to No V detracts from the value of the whole experiment.

The following results of the topical use of vegetable bitters afford less equivocal evidence of their antiseptic properties, and the results are perhaps not without intrinsic value.

Salicylic acid has been successfully used by many as a dressing for ulcers. We have tried it in the treatment of

soft chancres which failed to yield to more ordinary treatment. At first we put a layer of dry salicylic acid over the sore and covered it with a bit of dry lint, or in one or two cases merely brought the foreskin over the part. This preliminary treatment causes considerable smarting, but for no great time. We leave matters thus for 6 or 8 hours, at the end of which time the sore is generally found to be very much improved in appearance The sore is now dressed twice daily with a lotion containing from 5 to 10 grs of Salicylic Acid to the ounce of Solution of Borax. All the cases, six in number which we subjected to this treatment proved remarkably successful. If the parts round the sore become irritated it is necessary to reduce the strength of the lotion.

Thro the Kindness of my friend Dr Wm Macfarlane of Merryflatts Poorhouse about a dozen cases of various kind

of chronic ulcers were treated with Strychnine. The lotion used was ½ an ounce of Liq. Strychniae B.P. in 8 ounces of water or oil. (Sometimes the strength of the lotion was reduced when there was apparent need.) The decision we came to as to the Strychnia lotion was that, as a rule, it was as efficacious as the ordinary red wash, and in one case, that of a large chronic ulcer on the leg, which had been tried with all sorts of treatment, it effected more good than anything that had been previously tried. For chronic ulcers that improve under frequent changes of dressing, Strychnine, on further trial, is likely to prove an addition to the many useful remedies we have at present in use.

A few cases have been treated with a lotion of Quinine, 1 gr to the ounce. The ulcers so treated have rapidly become clean & taken on healing action.

Powdered peruvian bark has been used by others to clean foul ulcers, but Roper inclines to give the credit of the good results which followed to the tannin which the bark contained. In our cases, however, a question as to the healing agent can hardly arise for with the exception of a very small quantity of acid to maintain solution of the alkaloid the Quinine was the only active ingredient in the lotion.

We shall now bring forward some evidence in favour of the view that Quinine & its congeners exercise antiseptic powers when introduced into the system.

It used to be generally supposed that this group of drugs acted primarily on the nervous system, and we find Pareira ranking them in the class Neurotics; Subclass, Cinetics. However the opinion is gaining ground that they are in reality blood-medicines

and that they necessarily influence the composition of the blood, before they affect the nervous system. Dr Headland in his specific action of medicines (pages 147 et seq.) places them in the general group Hæmatics & in the order Restaurantia. Dr Bartholow of Ohio in his new book of Mat: Med & Therap. published 1876 also calls them Restoratives. We think that facts are in favour of the last-mentioned authors. The following are some of the reasons which induced Dr Headland to classify them as he did, and they seem to us eminently satisfactory.

1st Tonics (meaning thereby all the medicines which we have mentioned as being included in this group except Strychnia. We of course include strychnia) are not quick & sudden in action.

2nd Their effect is not transitory.

3rd Debility, the disease which they cure, is always in the first instance traceable to a want in the blood and is cured

by improving the blood.
4th Ague is a blood disease.
5th Quinine or a substance chemically identical with it (he should perhaps have said indistinguishable from it) exists in healthy blood. (page 150)

Leaving out the last mentioned statement, the other four form a very complete argument, but the fact that a quinoid principle has been found in healthy blood is a powerful corroboration of the truth that Quinine & its neighbours are blood-medicines. Here let us consider what we know about this quinine-like principle ~~of~~ animal quinoidin as it has been called.

Dr Bence Jones in a lecture, delivered at the Royal Institution in April 1866 says that, when he and Dr Dupré, were experimenting with a view to ascertain the rate of passage of quinine into and out of the textures of animals, they found, to their great disappointment at first,

that in the textures of a guinea-pig which had taken no quinine, there was a substance almost exactly similar to quinine. They first discovered its presence by the "fluorescent test" of Prof Stokes and, though they were unable to separate it, they found that a solution of it responded to all the other chemical tests that are used for quinine. They therefore concluded that it was an alkaloid and was closely related to quinine.

Without following Dr Jones through all the details of his investigation we may say that he has found that there exist close chemical relations between the bitter vegetable principles and Taurine a principle obtained from the bile. This of course makes quinoidin stand in near relation to the bile. In favour of the view that bile and quinoidin are closely connected we have the facts that bile has

antiseptic properties, is bitter to the taste and when administered internally is tonic in its effects, and quinine the alkaloid that the so-called ~~alkaloid~~ animal quinoidin so much resembles has likewise all these characteristics. Further we know that the bile, though it is thrown in large quantity into the intestine, does not pass out with the faeces, but, after undergoing certain chemical changes, is resorbed into the circulation; and that though the bile or its essential constituents, ~~though they~~ are resorbed, they are not to be found in the blood as such, but in their stead is found this nitrogenous compound quinoidin. Nothing definite is known as to the ultimate destiny of the resorbed bile. Liebig gives as the elementary composition of bilin 76 atoms of Carbon 66 of Hydrogen 22 of Oxygen 2 of Nitrogen and a small quantity of Sulphur

(the sulphur is supposed to be oxidised before the biliary constituents re-enter the circulation.) The small proportion of ~~the resorbed bile~~ Nitrogen present makes it unlikely that resorbed bile is used for the formation of tissue. It is probable that it remains in the blood and becomes slowly oxidised thereby producing heat. If however the view be correct, (and we think it is) that this resorbed bile is identical with Bence Jones's Quinoidin, and if its function be what we suppose it to be, its effect is not so much to produce heat as to check the over-production of heat.

The consideration of the function of Quinoidin in the blood involves an inquiry into the nature of the changes which are constantly taking place in the blood and tissues, and it cannot be altogether dissociated from the consideration of the specific action of the group of drugs which Quinoidin

so closely resembles.

We shall try to show that the processes of repair & waste which are constantly going on in the tissues & blood are fermentive in their character, and that quinoidin, quinine &c in the blood act as antiferments or antiseptics. To prevent misunderstanding it is well to see what meaning we attach to the words 'fermentation' and 'antiseptic'.

Fermentation is a name which has been given to certain peculiar chemical decompositions depending on the growth and multiplication of certain minute organisms, which have been termed ferments. In order that fermentation go on it is necessary that the ferment be in a suitable ambient medium, at a temperature within certain limits and containing proper food for the organisms. The development of a given ferment is always followed

by the same general results.—
e.g. in vinous fermentation we have the Torula Cerevisiae growing, and Alcohol, Carbonic Acid &c being produced; and it does appear that the chemical changes which occur are the direct consequences of the physiological growth of the ferment.
We believe that we have a parallel to all this in the tissue changes in the human body. A very small mass of Torula Cerevisiae soon becomes a mass of considerable size. A human germ cell and a human sperm cell meet under favourable circumstances and in process of years we have an adult human body. It will be said there is a difference. There is a difference, but there exists nevertheless a true analogy between the two processes. It is true that in the former case increase of bulk merely means increase of numbers

of the original Torulae

of the original Torulae, while in the latter case we have for the human organism, a something different from either germ or sperm cell. It is none the less true however that in the latter case, as in the former, we have descendants of the original cells, (though somewhat metamorphosed) existing as separate entities. The torula is repeated in the torula, while the germ cell & sperm cell are represented by the connective tissue corpuscles, blood corpuscles and other cellular bodies. The "ferment guid" formed in the process of growth of the yeast plant is alcohol, carbonic acid &c; that in the other case is urea, uric acid, Carbonic acid, water &c. The difference between the two cases is that in the former the organism never develops into anything beyond the torula, and the effete torulae are represented only by

unorganised albuminous débris, while in the other case there is the human body, made up not only of actively living organisms but also dying & dead representatives of the original sperm & germ cells. In both cases, however it is the activity of the minute organisms which ensures the perpetuation of the existing state of matters, and this, we think, makes good the analogy between them.

As we have already implied we look upon the whole of the cellular elements of the tissues of the human body as a ferment, or a number of different kinds of ferments, by whose development the changes of tissue formation and waste occur, but in order to maintain simplicity, we shall at present take the colourless blood corpuscles only as representative, and this we the more readily do when we consider that all the cellular elements have a

common origin. The colourless blood corpuscles are identical with the lymph & chyle corpuscles. They first appear as corpuscles in the lymph, as it issues from the lymphatic glands, and they probably take their origin in the lacunae in the alveolar tissue of the lymphatic glands (Kirk's physiology) These lacunae contain nuclei and these nuclei together with similar cytoblasts in the spleen and other ductless glands may be looked upon as the earliest known form of this ferment. This then is the known history of the little organisms we have under consideration. The elementary cytoblasts become colourless blood corpuscles in the lymphatic glands the colourless corpuscles or the nuclei they contain develop into red corpuscles which in turn become effete and die. The corpuscles run their race in the blood stream; while pale

they perform amœboid movements & as red corpuscles they carry oxygen to the tissues, and finally they find a resting place in the spleen where they become disintegrated. It seems pretty certain that they die in the spleen for in that organ débris of corpuscles is found (Kirk)

In the blood corpuscles, then, we have little organisms living active lives, and coincident with, and consequent upon this, we have chemical changes going on in the body, the results of which may in general terms be said to be the formation of urea, carbonic acid and water. In other words we have albumen, fat, sugar, starch &c being transformed into Urea, CO_2, H_2O &c the transforming medium being the corpuscles. This we think, looks very like what is called outside of the body, a process of fermentation.

Recent researches have quite

accurately demonstrated the nature of the action of quinine on certain constituents of the blood. It arrests the amoebiform movements of the pale corpuscles, and it affects the function of the red blood corpuscles as carriers of active oxygen and thereby diminishes the oxidising power of the blood (Bartholow p. 127)

Now we seek to show that this action of quinine is the action of an antiseptic in the ordinary sense in which the word antiseptic is used. It is not easy to give a definition of an antiseptic that would be generally admitted to be correct However in a lecture by Dr Burdon Sanderson pub. in the Brit. Med. Jour of 5th Jan 1878 it is shown that the substances most generally recognised as antiseptic, Chlorine, Potassic Permanganate Carbolic Acid &c are such, not in virtue of their directly neutralising any poisonous matter already formed, but by destroying the bacteria or other

organisms which by their development form such material, and so stopping the production of septic matter. An antiseptic then is a substance which is hostile to minute organisms, and we think the action of quinine in attacking the colourless blood corpuscles and lowering their vitality gives it a real claim to be considered antiseptic.

When quinine is found to attack the developed corpuscles and lower their vitality it is impossible to believe but that it acts with equal or greater severity on the rudementary forms or germs of the corpuscles, killing off many of them before they attain development. In the blood or out of it quinine is found to be germicide, antifermentive or antiseptic, and considering the near approach to identity which exists between quinine & quinoidin, we think it may fairly be allowed that these terms apply likewise to quinoidin

It is quite possible that an antiseptic be present in a fluid in such quantity that, though it be not strong enough to kill the ferment at work in the fluid it is sufficient to check the rapidity of growth and multiplication of the ferment, and so to affect the products of fermentation. This is the state of matters we conceive to exist in the blood. We have the corpuscles restrained in their activity by the quinoidin.

We shall now consider some of the diseases in which the vegetable bitter tonics have been used and see how far their therapeutic action compares with the known physiological effects of quinine and whether the theory that we have been advocating agrees with the facts that may be brought forward.

In Debility we have imperfect nutrition owing to depraved blood.

In most cases we have the corpuscular elements of the blood increased in quantity and imperfectly developed and there is a tendency to the formation of abscesses. The administration of quinine rectifies this state of matters, improves the composition of the blood and so improves the general health. The fault in Debility probably is that there is an insufficient amount of quinoidin naturally present in the blood, and this admits of the too rapid production and imperfect elaboration of the corpuscles. The curative action of the quinine consists in permanently increasing the quinoidin and that this is the case is proved by the permanently increased fluorescence of the blood following the administration of quinine. (Barthelow p. 128)

Quinine has been used with more or less success in various diseases

a prominent feature of which is fever. Fever is, in essence, the over oxidation of the tissues, and is characterised by an increase of the fibrin and of the corpuscular elements of the blood and by more or less paralysis of the sympathetic System. In some cases the nervous system is first affected and the blood secondarily while in other cases the reverse holds good. Fever where the nervous system is first at fault is usually brought about by the influence of cold or damp. In local inflammations accompanied by fever cold and damp are supposed to cause more or less prostration of the sympathetic, and the altered nerve influence thus induced affects the corpuscles either directly or indirectly, so that both the local lesion and the general inflammatory condition occur. Both the local inflammation and the general fever may be looked

upon as results of certain physiological processes carried to extravagance or excess. Over activity of the blood corpuscles with concomitant over oxidation of the tissues is the furthest point to which we can press our observations. If the action of quinine be what the theory advanced says it is, we should expect good from its administration in such circumstances And this we do get. So long as the corpuscles have not left the blood stream local inflammations and their accompanying fever are likely to be controlled by quinine. Dr Barthelow says that 'a commencing fibrinous pneumonia pleuritis or endo 'carditis may be suppressed by a full dose (15 to 20 grs) of quinine".

Vegetable bitter principles are of use in many diseases in which the fever is due to the presence of a poison in the blood. The poisons may be generated in the system

as in Rheumatism but more frequently it is introduced from without. Of persons introduced from without some spend themselves in bringing about the disease e.g. Ague, while others by the very act of attacking the victim, multiply themselves so that the fever stricken person is a fresh centre for the propagation of the disease.

The prominent fact which connects Rheumatism with our present subject is the wonderful success which has attended the use of Salicin and Salicylic acid in Rheumatic fever. It is true that chronic Rheumatism is often treated successfully by Quinine in combination with some such catalytic as Iodide of Potassium, and that acute Rheumatism has been & still is sometimes treated by the administration of very large doses of quinine, but the results are not so uniformly successful as to allow us to generalise on the subject

The last two or three years experience however has shown that Salicin and the Salicylates in many cases of acute Rheumatism, act as a kind of specific, and in the great majority of cases they shorten the attack. This is a generally acknowledged fact but the same certainty does not exist as to how the good result is accomplished. Two inquiries are involved 1st As to the nature of Rheumatism and 2nd As to the action of the drug. We do not propose to be able to throw new light on the matter. What we seek to do is to show that there is no evidence existing which runs counter to the views we have been advancing. What the poison of Rheumatism is, or whether indeed it have a poison we cannot at present say. We know that Rheumatism is a specific inflammation and that there occurs with it an over-production of Lactic acid; but whether

we are to look upon the Lactic Acid as a cause or a result we cannot say. I do not know that there is anything known of the etiology of this disease which contradicts the following; As a rule an attack of Acute Rheumatism follows upon exposure to cold or damp, and this being the case, we may look upon altered nerve influence as the first pathological effect. (This does not set at naught the indisputable fact that certain persons are specially liable to be ~~attacked~~ affected by Rheumatism.) This changed nerve influence, in a way not understood, may cause the nitrogenous tissues to be oxidised too precipitately and in such a manner that large excess of Lactic Acid accumulates in the blood. Such a fault or kink in the breaking down process of the albuminous principles, when once begun would

act so as to increase itself. In the state of health the albumen breaks down in such a way that part of it in the process of oxidation forms guanoidin. Now guanoidin is stable, not very easily oxidised, and at the same time its presence retards the oxidation of other substances. If through any ~~metamorphosis~~ irregularity in the tissue metamorphosis guanoidin should fail to be formed there would at once occur a double cause for the production of a high temperature suddenly coming on such as we have in Acute Rheumatism. According to this hypothesis the excess of Lactic acid would be mainly accounted for by the too precipitate oxidation of the nitrogenous tissues.

I am aware that Lactic acid is generally formed by the oxidation of the non nitrogenous food but it is not unreasonable to suppose that,

under certain circumstances, albumen may be so oxidised as to form it. Outside of the body we have Lactic acid formed from a nitrogenous compound. Alanine is decomposed by nitrous acid and gives Lactic acid nitrogen & water.

$C_3H_7NO_2 + HNO_2 = C_3H_6O_3 + H_2O + N_2$ (Roscoe)

Further evidence by analogy in favour of the possible formation of Lactic acid from albuminous principles in the case of Rheumatism is found in the formation of glycogen or animal starch in the liver in the state of health. Bernard & others (vide Kirks Physiology page 338) have shown that this ternary compound (glycogen) is formed "even out of principles in the blood which contain no trace of saccharine or amylaceous matter". If, indeed, Rheumatism be caused by the nitrogenous principles missing some of the earlier steps of oxidation, the early products

of the oxidation of albumen will as a consequence be absent from the blood or present in diminished quantity only. Now we know that these early products as represented by quinoidin exercise a restraining power over oxidation, and in Rheumatism with its over-oxidation we should expect good results from the introduction into the blood of a substitute for quinoidin. Such a substitute we believe we have got in the principles extracted from the willow. Why Salicin and Salicylic Acid are so much more useful in Rheumatism than Quinine is, we do not know, but these principles are very near neighbours to Quinine. The principles from the willow are bitter to the taste and Antiseptic like all the other members of the group under consideration; they differ however from all the others in being non-nitrogenous in their chemical composition. On account of their ~~not~~ containing

no nitrogen it might be said that they cannot be considered substitutive of guinoidin in the sense that guinine is. I am not chemist enough fully to combat this objection but the following isolated facts seem to go a great way towards meeting it. Indigo a nitrogenous body $C_{16}H_{10}N_2O_2$ is sometimes found in apparently healthy urine. Indigo when treated with caustic potash gives Salicylic acid. (Roscoe). Now there is free soda in the blood and this with the other two facts allows us to infer that it is not impossible that Salicylic acid itself may be one of the stages in the downward process of oxidation and that if it do not contain nitrogen it is but one step in the ladder from containing it.

The powerful curative influence

which Quinine exercises over intermittent fevers makes it, second only to opium, our most trusted weapon against disease. We shall not take into consideration the question whether the poison of ague be an organism or not. Such an inquiry would have no bearing on our present purpose. In any case great increase in the numbers of the colourless blood corpuscles & hypertrophy of the Spleen, the principal organ which has to do with their elaboration, are the chief pathological effects of the poison. In the physiological state quinine represses the activity of the corpuscles and its specific action in ague quite corresponds with this. Through the influence of the fever poison the natural ferment of the blood is stirred up into undue activity, and the introduction of something into the blood to regain the hold that

the natural antiferment, Quinoidin has lost, is what we should look to to rectify matters. This is exactly what Quinine does; it is the supplementary antiferment opposing the undue activity of the corpuscles. The wonderful prophylactic influence of Quinine in ague may be similarly explained. The alkaloid in this case forearms the corpuscles against the attacks of the poison.

Quinine has been frequently used in infectious diseases but reports of its effects have not always been satisfactory. We are not however without experience of its benefits in diseases depending upon the presence of organisms in the blood. The alkaloid is of great use in Septicaemia. Bacteria are invariably found to be present in the fluids which give rise to Septicaemia and the fermentation which takes origin from the presence

of these organisms may be said to be the cause of the disease.

It must be acknowledged that the treatment of fevers by Quinine has been upon the whole disappointing. Still the failure is not complete for we have Dr Peter Wood (On the Successful treatment of Scarlet Fever" Churchill & King) saying that since he has adopted the giving of Quinine systematically he has not had a death from Scarlet Fever among cases that he saw early.

The comparative non-success which accompanies the treatment of Continued fevers by quinine is the bit of evidence most condemnatory of the theory advanced as to the action of this group of remedies. We know we have come far short of establishing the theory on a firm basis of proof. We never hoped to prove it. We aimed merely at stating it & showing what evidence there was

in favour of it. On the other hand we do not admit that the failure of Quinine in fever <u>disproves</u> it. Has not Quinine been trusted to too much to the exclusion of the other members of the group? What we want is an antiseptic which, without interfering with the vital functions, can be introduced into the circulation in sufficient quantity to check the fermentive process set up by the fever. If Quinine have failed should we not look to its neighbours? A priori, we might expect more good from Strychnia, seeing that, in the physiological state Quinine causes marked Cerebral disturbance while Strychnia interferes but little with the brain. Are there not grounds in what has been said, which would justify a trial of the treatment of fevers by Strychnia.

or some of the other bitter principles? But even supposing the result were failure, partial or complete, we must not lose sight of the possibility that that failure may be due to the fermentive process being stronger than could be counteracted by the amount of the antiferment that we felt justified in introducing into the system. We might still look hopefully to Quinine, Strychnine Salicin and their Congeners as being probably useful as prophylactic of Fever. It is said that "prevention is better than cure"; it is no less true that prevention is easier than cure, and we conceive it quite probable that after tonics have failed to cure fevers, their presence in the blood as non irritant antiseptics might prove prophylactic of them. "Possession is nine points of the law." If the fever ferment

be in the blood first it may be very difficult or impossible to stay its progress by the introduction of any antiferment. If, however, the antiferment be first in possession the hostile germs may be altogether withstood. Sir Thomas Watson in a recent paper in the "Nineteenth Century" on Zymotic diseases expresses a firm belief that in a generation or two all such diseases will have been made to disappear from our midst. Few of us may have the optimism of the veteran physician, yet events are assuredly moving in the direction of his expectations. Much has already been done by vaccination, sanitary improvement and rational treatment, towards weakening the vitality of the enemy, but surely it is not unreasonable to prope about for a weapon with which to strangle him in his birth.

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