On febrifuges / by C. Binz.

Contributors

Binz, Carl, 1832-1913.
Royal College of Surgeons of England

Publication/Creation

[London] : The Practitioner, 1876.

Persistent URL

https://wellcomecollection.org/works/q9k9ve2j

Provider

Royal College of Surgeons

Wellcome Collection
183 Euston Road
London NW1 2BE UK
T +44 (0)20 7611 8722
E library@wellcomecollection.org
https://wellcomecollection.org

4

ON FEBRIFUGES.

ON FEBRIFUGES.

BY C. BINZ, M.D.,[1]

Professor at the University of Bonn.

[*Reprinted from* THE PRACTITIONER *for* JUNE 1876.]

QUININE.

WE have seen that to alcohol belongs, not only the indisputable property of dilating the vessels of the skin, and thus promoting the irradiation of warmth in fever, but, in all probability, that of checking the activity of the cells as well, and in this way directly diminishing the production of heat in the tissues. In quinine and salicylic acid we have antipyretics, which probably exhibit only the latter action.

Nowhere was the neurotic theory of fever more clearly reflected than in the manner in which the action of quinine was formerly understood. Quinine was a tonic, nothing more nor less; that is to say, it gave the nervous system strength to resist the fever, and for that reason the latter disappeared, sometimes rapidly, sometimes slowly.

Facts, however, all speak against this one-sided conception of the matter. Ague, for instance, is to be regarded as the fever in which quinine gives the most brilliant results. It arises from the absorption into the system of a specific poison which develops itself from decaying vegetation. If this poison circulates too long within the body, decomposition of the blood is the result. Among the phenomena presented by the disease, the "neurotic" febrile symptoms may be entirely wanting, while the appearances depending upon degenerative changes in the blood and

[1] In the two preceding numbers, LOND. has been erroneously placed after Professor Binz's name, on account of a misreading of the word Bonn.

in the tissues, never fail to show themselves, though at the beginning they are often only slight.

Now, the notion that the nerves should be able to resist or to destroy any putrid matter by the help of quinine, is quite unintelligible according to our present knowledge of such things. First of all, we see that ague is cured by quinine most efficaciously in the time of apyrexia, when the infectious poison is latent, when every part of the nervous system is free, when neither heart nor respiration shows the slightest disturbance. Besides that, experimental researches have failed to demonstrate the presence of any such influence of quinine upon the nervous system as it has been supposed to possess. The influence of quinine over the febrile process in general may take place without the brain being at all acted upon. Thus, section of the spinal cord at the level of the first cervical vertebra does not prevent this antipyretic influence from being manifested, although, in that condition, not only is the brain separated from the cord, but the chief vaso-motor nerves are paralysed as well.

The diminution of reflex excitability in the nervous system, so much spoken of as having been observed in animals treated with quinine, has been proved by recent and strict investigations made in my laboratory to be purely imaginary.[1]

In former times, before it was known how fever can be produced artificially, one used to remark the improved condition of the fever patient after a good dose of quinine, and to attribute it to the "neurotonic" action of the drug. To-day, we know that this improvement depends upon a decrease in the oxidation and disintegration of the elements of the body, as especially shown in the much lower percentage of urea contained in the urine discharged after a dose of quinine. And as the absorption of certain ferments is evidently the cause of many fevers, it was worth while to investigate whether this agent has any specific power over them.

After the isolation of the various alkaloids from their respective drugs (dating from the year 1816), when it was found by experiments upon animals that these substances, even in very small quantities, all exerted an influence either upon nerve-centres or

[1] Heubach, *Archives of Experimental Pathology and Pharmacology*, vol v. pp. 1-38. (Leipzig.)

upon nerve-trunks, this property came to be regarded as one belonging to alkaloids in general, and thus quinine, discovered in 1822, easily got the same reputation. No doubt it possesses a striking family resemblance to these nervine alkaloids. It differs from them, however, in one important point and in a very remarkable degree.

All the other alkaloids in common use act in very small doses; caffein, which possesses this characteristic least of all, produces its characteristic effects even when given in a dose of a few grains. Quinine, on the contrary, given in minute quantities, like morphia, strychnia, atropia, is absolutely indifferent as regards any effect produced. The hundredfold of such doses is the quantity in which it must be taken in order to bring about the result it is desired to obtain.

This striking difference ought to have given a hint as to where to direct the researches in connection with quinine. Pringle, in 1750, made a beginning with cinchona bark only, which, if followed up, would have given results of great importance, but the nerve theories appeared, and soon stifled these valuable experiments.

Quinine is a powerful antiseptic and antizymotic, possessing decided advantages over all other agents of this class. It can be given in large doses,—it remains in the circulation for many hours,—it does not enter into combinations or undergo decomposition within the organism so as to become a thing chemically indifferent with respect to the ferments upon which it is desired to have it act. When given once a day in a dose that is not of itself too small, it circulates through the tissues, keeping them constantly under its influence.

An agent which acts antiseptically outside of the body cannot fail, under such circumstances, to exhibit the same action within it. Ague derives its origin from septic processes occurring in the blood and tissues, and if the disease progress unhindered, it will in many cases finally destroy life with all the symptoms denoting decomposition of both. If brought into contact, without the system, with the exciting cause of ague—which, as we know, is a ferment arising from decaying vegetation—quinine will paralyse the further chemical development of the ferment itself, just as it paralyses the activity of processes set up within

the body by this subtile agent, unknown as to its precise nature, but well understood in its effects.

Quinine has no permanent influence upon the temperature of the body in health, although it often produces a distinct change, as well as causing a decrease in the amount of urea excreted. We need not recur to any nerve theory to explain this. Quinine has a very strong affinity for many septic ferments, but a very slight one for the ferments of the healthy organism, as can easily be proved by experiment. Therefore, wherever it encounters one of the former in the course of its circulation, it manifests this affinity, paralysing the activity of the pyrogenic substance, so that, as a result, a change of temperature is clearly shown by the thermometer; but wherever these septic ferments are absent, this result will, of course, be much less perceptible.

If one severs in a living dog all the nerves leading to the spleen, quinine nevertheless acts on that organ, causing it to shrink. The spleen is the chief source of the formation of uric acid. Quinine lessens the quantity of this acid produced by a healthy man very strikingly. As the afferent nerves of the spleen are not necessary in order that this action may take place, we are induced to accept as an explanation of the same, the probable occurrence of a chemical process in this instance also. This conclusion is especially justifiable, as the spleen contains an immense number of white cells, for which quinine is a highly efficacious poison. They are the seat of energetic oxidation, and this oxidation is lowered by quinine.

In febrile processes the spleen becomes swollen in consequence of the irritation it receives from the pyretic substances that circulate in the blood. Now if the activity of these substances be diminished by any means, it follows that the effect they have contributed to produce will also experience a diminution, and nature once more exerting her supremacy, the spleen will shrink to its normal size.

The decline of temperature in fever, so generally induced by quinine, takes place independently of any connection with the performance of the heart's functions. It very often happens, in fact, that a change in the action of the heart only *follows* such

a decline. The same is true with regard to the function of respiration.

Of all that has hitherto been said, especially in France, about the antipyretic action of quinine through the medium of the vessels, nothing has as yet been proved, and the evidence against such a theory is abundant.[1]

In the March number of this periodical I read a very interesting article on the treatment of sunstroke by the hypodermic administration of quinine. Dr. Hall thinks that quinine acts here as a stimulant to the vaso-motor and the inhibitory nerves. Dilated capillaries in sunstroke may be produced by stimulation of the inhibitory centres and depressor nerve of the heart, or by exhaustion of the vaso-motor centres. Quinine may reduce the temperature of the skin by exalting the action of the inhibitory apparatus, and allowing the vaso-motor centres to produce contraction of the blood-vessels; or may act as a direct stimulant on the vaso-motor centres themselves.

The author of that paper mentioned my name in connection with this view. He must have misunderstood me, as after all my experiments,[2] I am more than ever convinced that we have no right as yet to such opinions.

The essential cause of sunstroke is overheating of blood and tissues, and therefore decomposition of the nutritive material. The blood acts as poison on the heart and the nervous system. Should the treatment recommended by Dr. Hall prove applicable to all cases, we must assume that here also quinine acts as a direct antizymotic, as it does in malaria fever.

Numerous are the instances in which it has been shown that quinine acts directly on protoplasm, and without any agency of the nerves being involved. Take, for instance, two similar specimens of any protoplasm which is known to undergo rapid oxidation when exposed to the air, and add a very small quantity of quinine in a soluble form to one of them. The difference of effect produced upon the two by the oxygen of the air will soon

[1] It would exceed the space at my disposal were I to enter into experimental details. I have summed them up, with references to the different literary sources in my pamphlet: *Das Chinin, nach den neuren pharmakologischen Arbeiten.* Berlin, 1875.

[2] *Archiv f. exper. Pathol. u. Pharmakologie.* December 1875.

be observed, the quinine checking the combination completely where it has been applied. One of the most striking examples of this anti-oxidizing power is shown in the following experiment.

Place a piece of a fresh sea fish in sea-water, and after a certain time, depending upon the warmth of the season, before any putrefaction takes place, the whole becomes brilliantly phosphorescent. There can be no doubt of the fact that this phosphorescence is derived from the energetic oxidation of the numerous infusoria contained in the fluid.[1] This luminous water is next put into different test-tubes and acted upon successively by various antiseptic agents, beginning with a very small quantity of neutral quinine (1 to 5,000 or more), then by a very weak solution of carbolic acid, and by the different neutral salts belonging to the class of antiseptics, all, of course, dissolved in distilled water, and experimented with in a perfectly dark room. Quinine is then found to surpass them all in the energy with which it causes the phosphorescence to disappear.

If it were claimed that quinine is incapable of acting chemically upon living cells in such a state of dilution as it circulates in the body, the above experiment, among others, would prove the contrary. Only one must not expect to obtain a quite sudden effect, using such minute proportions, nor do we expect anything of the sort in the case of a fever patient to whom we administer such doses. If it be desired to destroy the oxidability of the sea-water infusoria within half-an-hour, one may take quinine in the proportion of 1 to 12,000; if in a few minutes, 1 to 2,000; if in an instant, 1 to 200. Agitation of the previously luminous liquid with air, a proceeding which would otherwise revive the phosphorescence of the protoplasma, then fails to produce this effect.

I should not like to be misunderstood, however, with respect to the purpose for which I have introduced this illustration, for I do not in the least pretend that such animalculæ are in any way involved as the exciting cause of fevers, but have merely taken their protoplasm as *one* type in which quinine exhibits, in a striking manner, its anti-oxidizing power, just as in other experiments it shows an antizymotic one.

[1] For evidence bearing upon this point, see Pflüger's *Archive für Physiologie*, 1875, xi. 222.

All these questions, of course, as to the precise manner in which quinine produces its antipyretic action, can only be settled when we shall have become better acquainted with the nature of pyrogenic poisons. Here I can do no more than point out the path which, if followed, promises to lead to the desired knowledge on this subject, and at the same time to show how the theory formerly offered in explanation of the same only led us into a "blind alley," so to speak, from which there was no exit but to retrace one's own footsteps.

Knowing at some future time the different agents concerned in the production of each separate form of fever, it will be easy to understand how it is that quinine is so extremely efficacious in ague, while it fails completely in relapsing fever; why it acts with such decided antipyretic power in *Typhus abdominalis*, while it seems to be useless in *Typhus exanthematicus*, and so on.

The well-marked action exerted by quinine in solution, upon many septic ferments on the one hand, and its indifference toward the protoplasm of *Penicillium glaucum*[1] on the other, may serve for the present as an instance illustrating by tangible examples the puzzling inequality of effects produced by this drug upon fever-producing ferments within the human body.

As to the nervous system, I do not pretend to claim that quinine is entirely without influence upon so important a part of the animal mechanism, for sleep is often produced by a dose of quinine in a non-febrile illness, and certain neuralgic affections are known to be completely under its power. Like alcohol and calomel, therefore, quinine may be said to possess a manifold sphere of action. As regards its efficacy in fever, we must once more confess our inability to explain all the facts taught us by therapeutic experience. But, as yet, the only theory which reconciles the results of such observations with the results elicited by experiment in the laboratory, is the humoral one.

I will conclude with some practical remarks as to the application of quinine in fever. It is to be given (1) in large doses from 0·5 to 3·0 grammes (8–48 grains); (2) in a digestible form, that is to say, together with some acid; and (3) during the time when fever tends to decrease.

[1] Cf. Virchow's *Archiv*, xlvi. 73.

The first has been proved by numerous observations in the sick-room. Such strong doses are not poisonous, but agree on the whole better with young than with old people. My second rule refers to the fact that in fever the stomach does not contain sufficient acid to dissolve the sparingly soluble sulphate. As to the hour of administration, we have to deal here, as a matter of course, with similar conditions as in ague fever. The cause of fever is overcome by quinine most easily when its activity is lowest.

The complaint has often been raised that quinine so easily causes sickness, and it is generally supposed that the vomiting is produced by direct irritation of the stomach. This is not proved to be the case. On the contrary, if the doses of quinine are continued, at the most only a small part of the second or third are ejected. All later ones remain. The stomach absorbs it as hitherto, the nervous system by degrees tolerates the alkaloid, and now only it begins to act upon the chemical processes of the feverish organism. It is very important not to make use of impure quinine. Quinine containing the less efficacious cinchonine is the most deceptive, for this adulteration is somewhat difficult to detect, at least for many practitioners. Much the same must be said of salicine, the bitter principle of willow.

By adding to a solution of *pure* sulphate or hydrochlorate of quinine a little ammonia, one gets a thick precipitate of hydrate of quinine. This is easily soluble in a little ether, whilst the hydrate of cinchonine remains.

The following test is applicable for *all* secondary alkaloids of Peruvian bark.

Put 1·0 gramme of the quinine salt into a test-tube together with 10·0 grammes water of about 15° C., shake and let it stand for half-an-hour. Then 5·0 cubic centimetres of the filtrate are gently mixed with 7 cubic centimetres of ammonia of about 0·96 specific gravity. If the quinine salt be pure, no precipitate whatever will appear.

The sulphate and the hydrochlorate of quinine must not be coloured by addition of concentrated sulphuric acid in any way. A red tinge indicates salicine, a black one sugar, etc. Both salts must of course be thoroughly soluble in a little water with very diluted sulphuric acid, as well as in common spirit of

wine. On a platinum spatula they must burn away without leaving any residue.

Salicylic Acid.

Salicylic acid is not only the newest of the febrifuges, but of all therapeutic agents up to this date. It is an agent, too, that is destined to occupy no transitory place in the long list of medicines. Known long ago as one of the component parts of the essential oil of the American *Gaultheria procumbens*, of our *Spiræa ulmaria* and *Monotropa hypopitys*, which oils contain it in the form of salicylic methyl-ether, it was formerly prepared from salicine, the bitter principle of the willow, from whence its name is derived. Salicine is decomposed by saliva or by boiling with diluted acids into saligenin and sugar, and saligenin wants only one atom of oxygen more to become salicylic acid. Subsequently it was successfully produced from carbolic acid. This well-known product of coal-tar has a very close relationship to salicylic acid, as the addition of one equivalent of carbonic acid to the formula of carbolic acid gives that of salicylic as shown in the following diagram :—

$$\underset{\text{(Carbol.)}}{C_6H_6O} + CO_2 = \underset{\text{(Salicyl.)}}{C_7H_6O_3}$$

The process, however, by which this transformation was effected continued to be rather expensive until a few years ago, when Professor Kolbe, of Leipzig, instituted a new and inexpensive process for the purpose, which is essentially as follows. He heats carbolic acid and hydrate of sodium together in a receptacle so contrived that a stream of carbonic acid is made to pass through the mixture, thus inducing the desired union of elements. The product so formed is the salicylate of soda, from which salicylic acid can be easily set free by any stronger mineral acid.

The salicylic acid of commerce is a yellowish white powder, having somewhat the odour of carbolic acid. In order to obtain it quite pure, it is necessary to heat the crude acid in a porcelain vessel covered over with filter-paper. The pure acid sublimes and attaches itself in the form of fine colourless needles upon the paper. One needs to apply the heat very cautiously however, since salicylic acid is decomposed at a higher temperature back into carbolic and carbonic acids.

The pure acid thus prepared has no odour, is of a sweetish taste, dissolves in about 300 parts of water, very readily in alcohol, ether, and chloroform, but most readily in water containing an alkali in solution; with the alkalies presented in this manner, it forms neutral salts.

Three properties possessed by salicylic acid seemed to Prof. Kolbe to give a guarantee that this newly-developed agent could be made to subserve a useful purpose in medical practice, viz.: first, that of its being a powerful antiseptic and anti-zymotic; secondly, because it can be taken in very large doses without producing symptoms of poisoning; and thirdly, because it remains a long time in the organism, and in its passage through is only partially destroyed.

The addition of a little perchloride of iron (Fe_2Cl_6) to the urine of a man who has an hour or two previously taken a few grains of salicylic acid, causes the appearance of a fine pink colour, the same as that given by mixing solutions of these two substances in pure water.

The first experiments with the new agent under consideration were made in Prof. Thiersch's surgical wards in Leipzig. He began by employing it instead of carbolic acid for the dressing of wounds after Lister's method, and found it to answer all his expectations. Over carbolic acid it possesses for this purpose the undeniable advantages of being less irritating to wounds and of having no disagreeable odour. Very soon afterwards, a number of experiments were made with the internal use of salicylic acid in connection with febrile diseases, principally in the clinic of Basel (Bâle) by Prof. Junnermann and Dr. Buss.

I shall not enter here upon any more minute discussion of the practical applications of salicylic acid, this branch of the subject having been fully treated of by Dr. Ewald, of Berlin, in the March number of this journal. We have now to do rather with the question as to how this agent performs its indisputable antizymotic action.

At first it seemed there could be no doubt but that the influence of salicylic acid in disease was one due entirely to a certain clinical affinity possessed by this agent for the tissues of the body and for the disease-producing ferments invading the

same. But then Salkowski[1] suggested that if salicylic acid becomes converted into the neutral salicylate of soda when mixed with a solution of the alkaline carbonate, this change must take place in the blood, and this neutral salt possessing little or no antizymotic power, how would it be possible to explain the antizymotic action of the drug by attributing the same to an energetic affinity of salicylic acid towards cells and ferments? To increase the perplexity, it was very soon found that the neutral salicylate of soda given instead of the acid itself possessed an antipyretic action in every respect as great as the acid, and was without its disadvantages, viz.: that of being almost insoluble in water, of impairing digestion, and irritating the bowels. A sharp discussion arose in consequence, the result of which has been to clear up the difficulties in a certain measure.

As far as my own observations extend, I am convinced that in the discussion upon the application of salicylic acid and the salicylate of soda to therapeutics, the participation of one important factor in affecting the mode of action peculiar to these agents has been allowed altogether to escape attention. Our tissues, as is known, continually produce carbonic acid, of which the blood, notwithstanding its alkalescence, holds a good part in solution, either in a free state or in combinations, from which the CO_2 is constantly ready to separate. *Now this gas, developed absolutely pure, possesses the power of setting free the salicylic acid contained in the salicylate of soda,* a fact the importance of which cannot fail to be apparent as offering an explanation of the paradox above mentioned.

Ether shaken up with a one per cent. solution of the salt leaves behind upon evaporation no appreciable deposit. Another portion of the same solution first treated with CO_2 at the ordinary pressure of the air and in a room of moderate temperature, and then agitated with ether, gives over to the latter the seventh or tenth part of the salicylic acid contained in its salicylate of soda. The same proceeding, if repeated, continues to result in a further liberation of the acid.

The *rationale* of this action is one easily seen into. The salt dissolves very freely in water, in ether but sparingly, and so

[1] *Berliner Clin. Wochenschrift*, 1875, No. 22.

remains by the former. The behaviour of the acid is itself just the reverse,—it goes over to the ether, and when this evaporates remains behind, partly in the form of elegant crystals, thus showing clearly that the CO_2 has set it free from its previous combination with the soda.

Also if one first adds to the solution of the salt a little of the phosphate and carbonate of soda, so as to represent the conditions present in the blood, and then leads in the stream of CO_2, the liberation of the salicylic acid succeeds in a manner equally well marked, only that the quantity set free is somewhat less than otherwise it would have been.

Putrefiable mixtures sufficiently diluted with water, as for instance urine with an equal volume of water, undergo putrefaction when exposed to the air much less readily if previously treated with salicylate of soda and carbonic acid together than after the addition of either of these alone. This difference of action may extend over a period of several weeks. The best plan is to arrange the experiment so that one will have four preparations under observation at a time: of these, No. 1 is to have nothing whatever added to it; No. 2 to be merely impregnated with CO_2; No. 3 with salicylate of soda; and No. 4 to have both this salt and CO_2. Here also we must suppose a liberation of the strong antiseptic to take place which is only overbalanced by the gradual development of ammonia in the liquid.

We see therefore that it is not admissible to designate the salicylate of soda as a substance chemically inactive within the organism. Of a salt which is known to be decomposed by CO_2 no one can *à priori* assert that it passes unchanged through the organism of man, where every tissue with which it is brought in contact by the blood is constantly eliminating carbonic acid in a nascent condition, and in such quantity as to reach an aggregate of 700 grammes in twenty-four hours for an adult.[1]

[1] This may also hold good for Palli's sulphite and hyposulphite. These salts are immediately decomposed under the influence of CO_2, sulphurous acid being set free. The opposition made by Braun and Bernatzik (*Wiener Med. W.* 1869, No. 100) upon this theoretical point is, therefore, certainly unjustifiable. They assert, namely, that neither in the circulation nor in the secretion of external wounds is it possible for free SO_2 to be developed from these salts, a claim which

For this bearing of the question it is of no consequence *how* the acid appears in the urine. In two cases of quite fresh acid urine I was enabled to isolate crystals of free salicylic acid from the liquid. In the one case Dr. Heubach, my assistant, had taken 1·0 gramme (15·4 grains) of the salicylate of soda, and in the other a patient of the medical clinic had received five grammes of the same preparation. The urine used for these experiments was obtained two hours after the administration of the drug in each case, and the quantities taken were respectively 35 and 50 cubic centimetres (1 and 1½ fluid ounce).

According to Feser and Friedberger it is not practicable to extract salicylic acid from simple blood by means of ether; the blood must first be rendered acid.[1] This also is no proof against the correctness of the above deductions relative to the intra-systemic decomposition of the salicylate of soda, for we do not know in how firm a combination with the albuminoid substances of the blood the salicylic acid may have stood, combinations which ether alone would be powerless to dissolve.

Our animal organism is by no means a simple alkaline combination, such as a solution of soda and basic phosphate of soda in water. Zuntz, who has studied the alkaline action of the blood upon litmus most thoroughly, takes the presence of *free* carbonic acid in the blood of all living animals to be an unequivocal fact. The oxyhæmoglobin performs certain functions of a free acid; and that all tissues actively engaged in destructive assimilation at least do not exhibit an *alkaline* reaction, and that they are in any case charged with carbonic acid, are facts which are partly proven and partly deduced as a necessary consequence from several other established facts.[2]

The behaviour of pyrogallic acid toward the organism also teaches that it is an error to regard this latter as a simple alkaline mixture of elements. Cl. Bernard long ago called

can only be correct in so far as it may be true, that the acid just developed is at once seized upon by the albumen present. The latter, however, then becomes a different body from what it previously was.

[1] *Archiv für wissensch. und prakt. Thierheilkunde*, 1875, Heft 6.

[2] Compare, among other authorities upon this point, Dubois-Raymond, *Berliner Monatsberichte*, 1859, 288.; Pflüger, *Archives of Physiology*, x. 312; Buchheim, *ibid.* xii. 326.

attention to the unchanged condition in which pyrogallic acid, a substance that oxydises with extreme rapidity in alkaline solutions, circulates in the fluids of the body. Under the guidance of Hoppe-Seyler,[1] Jüdell has further shown that pyrogallic acid taken by the human subject in a quantity of 0·5 gramme (8 grains) appears after two hours abundantly in the urine.

This behaviour would seem quite unaccountable according to the unconditional alkalescence theory, but it is easy to show by experiment what is at least one of the causes of it. Thus, if one makes a solution of pyrogallic acid alkaline, divides the whole into two parts, and leads a stream of CO_2 through one of them, the well-known rapid browning will then be held energetically in check, even though free access of the air be secured by keeping up constant ventilation over both preparations. For the rest, and to avoid the objection that the carbonic acid which escapes hangs upon the surface of the liquid, preventing the O_2 of the air from reaching it, and hence the retarded oxidation, let the one half of the pyrogallic acid solution be augmented by the addition of carbonate of soda one part, the other with bicarbonate of soda two parts, at a low temperature. The effect is similar to that obtained in the first experiment; for while the brown colour appears in the one preparation as soon as the Na_2CO_3 is added, it is only slightly indicated in the other, where an excess of CO_2 is present. The same difference of effects manifests itself if into one portion of a solution of pyrogallic acid that has been made alkaline one immediately leads a stream of air, while through another portion of the same solution a second current, consisting of oxygen 21 volumes per cent. and carbonic acid 79 volumes per cent., is made to pass. Here the quantity of O_2 presented is similar on both sides, while the effects are quite dissimilar.

Nothing necessitates us to regard the decomposition of the salicylate of soda as taking place in the blood: it is rather to be looked for in the acid-producing tissues. Nor is it by any means urgent upon us to locate the seat of the infective processes in the blood; on the contrary, the ferments which excite disease invade our system from without through the medium of the lymphatic vessels, as is shown by the manifold

[1] *Untersuchungen*, 1868, 422.

processes of inoculation with which we are acquainted. The very circumstance of the persistent swelling of the adenoid organs in infectious fevers points to these as the constant centres of the disease. But immediately after death the reaction of the lymphatic glands is *not* alkaline. Further, it is known what a quantity of acid substances the living spleen produces.

In attempting to analyse the antipyretic action of salicylic acid one need not confine oneself to the circumscribed idea of antisepsis. We know that free salicylic acid exerts an action upon an infinite variety of ferments. It also cures such diseases as are characterised by an increased production of heat without being of a putrefactive nature. In the one case as in the other, it will affect albuminoid substances, toward which it may have a special affinity, either altering their nature or checking their activity as ferments. That an influence upon protoplasm belongs even to the neutral salicylate of soda was demonstrated on certain bacteria under the experienced guidance of Dragendorff.[1] The power of this salt to paralyse the development of bacteria shows itself to be greater than that of either phenol, quinine, boracic acid, or alcohol, and almost one third as great as that of free salicylic acid. Therefore, even setting aside the possibility of salicylic acid being set free from it in the tissues, a compensation for the inferior activity of the sodium salt would be offered in the much more rapid absorption of the latter into the system.

The view that the salicylate of soda exerts its antipyretic power through the medium of the heart or the respiration, seems to me to be quite unsupported. It is an easy matter to show that dozens of poisons which are absolutely powerless against fever possess the property of causing a depression in both the circulating and respiratory systems. The temperature of the body *can be* influenced by these poisons, particularly if the action of any one of them is driven so far as to bring about collapse. In fact, I scarcely know how one would proceed in order to get actually no diminution of temperature with such powerful agents as these. With salicylic acid, however, or its salt exhibited in such doses as those commonly given with good effect, there can be no talk of collapse, except in cases where a

[1] L. Bucholtz, *Arch. für exper. Path. u. Pharmak.* iv. 32 and 80. (1875.)

spontaneous and sudden decline of temperature coincides with the reduction effected by the drug.

Ewald expressly asserts that an action of salicylic acid upon the pulse and respiration in both forms, as tried in Frerichs' clinic for antipyretic purposes, was almost entirely absent. Riess, Buss, and other observers give reports agreeing essentially with this. If the reports of these observers are not sufficient to completely negative the claim in question, it may still be said that nothing more than an *inconstant* primary influence upon both systems is unanimously spoken of. The same holds good with respect to an influence upon the perspiration. In a case in Wunderlich's clinic at Leipzig the temperature went down after salicylic acid from 105° to 94° F., without any visible alteration in the skin.[1]

Salicylic acid possesses in all outward respects a resemblance to quinine. It combats the malarial poisoning (Senator, Buss) —although less surely and effectually than quinine—during the period of apyrexia, where, as is well known, neither the pulse nor respiration necessarily need present the slightest abnormity. It is, like quinine, a powerful antizymotic, which can be introduced into the organism in large quantities, circulates there a considerable length of time, and is given off again—at least partially—in an unchanged condition. Even the ringing in the ears and the slight deafness characteristic of cinchonism are not wanting in connection with the medication with salicylic acid. A complete agreement between its behaviour and that of quinine toward certain disease-producing agencies, known, as must be confessed, only by their effects, does not exist. This we have already seen in speaking of intermittent fever. Acute articular rheumatism, a disease in which quinine avails so little and salicylic acid so much, furnishes a second and converse example. Considering the chemical dissimilarity of the two substances, it is not to be expected that there should exist a similarity between their modes of action on more than the general points involved. This general resemblance, however, is unquestionably present, and so we shall have to seek an explanation of the manner in which their therapeutic action is exerted in the same channels.

[1] *Archiv für Heilkunde*, 1876, p. 378.

I cannot dismiss the subject of antipyretics without referring to the class of emetics and purgatives which often yield decided antipyretic results. But as their mode of action on the whole is so indirect, and their effects as a rule so transitory, they are scarcely entitled to be reckoned as true febrifuges. And as far as I know, there has been as yet but little done experimentally in the way of explaining the exact method of their antipyretic power. Perhaps the most striking instance of a purgative acting as a febrifuge is that of calomel, as given with such marked success in incipient typhoid fever. Here it is almost certain that the calomel is changed into perchloride of mercury within the system, and this latter being one of the most powerful antizymotics that exists, would probably act directly upon the disease-producing ferments at work in the intestines.[1]

[1] In the former article, twelfth line from the bottom of p. 283, instead of *although* read *because*.