The Value of Antipyrin in Epilepsy and Epileptiform Convulsions

A Thesis

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Before entering upon the main subject of this thesis I should like to mention my reasons for trying Antipyrin in Epilepsy.

Early in the year 1888, on being appointed Assistant Medical Officer to the East Riding Asylum, I for the first time came into close association with this disease. My epileptic patients I believe interested me more than any other of the inmates of the asylum, and caused me to think a good deal about the disease from which they were suffering.

At this time Antipyrin was the fashionable drug, it was being used for almost everything. Nearly every week letters were appearing in the medical papers stating that it was a specific in the cure of some disease or other. To be followed a few weeks later by other letters denying it was of any use in the said disease at all, but that it was a certain cure for some other disease. Few or no details had been published as to its physiological action; I had therefore been trying to draw some conclusions for myself on this point. One of these right or wrong was that it stimulated inhibitory nerves.

As above mentioned Epilepsy had made a great impression on my mind; and thus it was that I came to wonder whether Antipyrin might not stimulate inhibitory cells which in this disease seemed to have lost their control. What I now
think its action really was will be considered later, but I think it is better to show that my reason for trying Antipyrin in Epilepsy was a rational one and due to some little thought: not merely a jump in the dark because it happened to be the fashionable drug at that time and was being tried for every symptom and disease.

just as I had commenced my trials of the drug, a note appeared in one of the medical papers saying that Antipyrin had been tried for Epilepsy in one of the Paris hospitals but with no benefit for the patients. Though much discouraged by seeing this I however continued my observations, with, I am glad to say, good results in some cases which I give below.

I intend dividing the following paper into four sections viz.

1. The cases in which it was tried, with dose and result.

2. The therapeutic action (as reported) of Antipyrin in diseases which have any bearing on Epilepsy.

3. The Physiological action of Antipyrin.

4. In what way Antipyrin acts in Epilepsy and Epileptiform convulsions.

The first thing I did was to take the patients on whom I was going to try the drug, off their Potassium Bromide for a month previously to giving the Antipyrin.

At first I intended to give the Antipyrin
continuously and compare the number of fits taken say in a month with the number of fits taken during the same time when no drug was administered. I did this in the case of a woman (case 30, see below) but in about ten days she began to get paranoid and to develop symptoms of a general paroxysm. The drug was then stopped and she quickly recovered her usual health.

I therefore gave up giving it continuously and had to pick my cases; trying on those in whom one fit was usually followed by others, and seeing if the drug administered after the first fit would stop the succeeding ones. Unfortunately there were not many cases in the asylum which fulfilled the above conditions; most of the cases only taking odd fits now and again, but there were some from whom I think I can fairly draw some conclusions. Of course the great difficulty in judging the efficacy of a remedy given in such a way for epilepsy is that you cannot be sure that the patient would take another fit if he did not get the drug.

The patient A. B. however was a singularly good case for my purpose as the sort of fits invariably lasted twenty-four
hours and often longer. The case C.B. is another from which I think conclusions may fairly be drawn as to the tend her fits chiefly at night and if she had one it was nearly always followed by others varying in number from two to eight a.m. 2.m. is also a good case.

Some of the cases in which Antipyrine was given, with dose and result.

A.B. aged 47, a chronic epileptic. She had been in an asylum for years and was beginning to get demented. The fits were as a rule of a mild type with loss of consciousness and tonic spasm, the clonic spasms however were not violent. The fits would follow each other in rapid succession and the bout invariably lasted the day and often the next. She would then be in a drowsy exhausted and semiconscious state for another day during which time she would take no food. On 16th Feb. 1880 she was convulsed and was given Antipyrine gr. 1/4 at 11 a.m.; within a quarter of an hour much to my surprise she was free from fits; she then slept for an hour, after which she got up and took her dinner. At 9 a.m. she again got Antipyrine gr.
after which she again quickly recovered and took her dinner. From that time, whenever her jits commence, she has always been treated with Antipyrin and it has never failed to relieve her by quietly stopping them. She takes her jits much less often than formerly, when she does she is now given Antipyrin which has seldom to be repeated. The jits leave her as a rule in about quarter of an hour; she can always take her next meal. After the jits she is bright and (for her) talkative, instead of being dull and comatose for twenty-four hours as she formerly was.

C.D. female, at 10, an epileptic imbecile. She takes her jits usually at night. In 1877 she took 758 jits, of which she took 593 at night and 165 during the day. She seldom takes a single fit at night, one fit being usually followed by at least one more, often from four to twelve more. Thus in January 1877 she took 65 fits at night, made up on different nights as follows: 2, 1, 4, 5, 9, 4, 2, 8, 6, 4, 7, 2, 2, 3, 2, 2. Instructions were given that she was always to take one fit before getting any Antipyrin, the trials were all made at night. 12 March 1877 she took one fit; was then given Antipyrin & had no more fits.
13 March. She took one fit; was given antipyrin gr XV and had no more fits.
14 March. Took one fit; was then given antipyrin gr XV but took two more fits. Here the dose was halved and was evidently insufficient.
16 March she took one fit and was then given antipyrin gr XV. She took no more fits.

As long as I tried her with the antipyrin I have no record of her taking a second fit, the same night after a dose of gr XV.
I had however to put her back on potassium bromide as she began to show some ill effects from taking so much antipyrin.

Here can how I think with little doubt that it had a contrary effect on the fits.

E.F., female, 40; suffering from chronic mania. She would at times take a bout of fits. On one occasion had had four severe fits in succession. I gave her antipyrin gr XV and she took no more fits. I was unable to try it on her again as she was removed to another asylum.

E.H., male, 35; suffering from chronic epileptic mania. He would take bouts of fits at intervals which would last over a day. He took one fit in the morning about 10.30, then was given antipyrin gr XV and had no
more fits till one p.m., between which hour and 3 p.m. he had 6 fits. He was then given Antipyrin gr XV again; after which he had no more fits but remained dull and comatose for about an hour.

9 Aug. female, aged 27, suffering from Chronic Epileptic Mania.

14 July she took ten fits; was then given Antipyrin gr X and had no more fits.

6 Aug. she had 15 fits during the day; she was then given Antipyrin gr X; she had no more fits and passed a good night.

9 Aug. she had a bad fit in the morning and was given Antipyrin gr X and another gr X in the afternoon; in spite of which she had 22 fits up till bedtime when she was given another gr X. She passed a rotten night but took no more fits.

10 Aug. No more fits. 11 Aug. No more fits.

13 Aug. The fits began again in the morning, she was then given gr X which stopped them for a time; but they recommenced in the afternoon when she was again given Antipyrin gr X; after which she passed a quiet night and had no more fits.

14 Aug. No more fits. She was free of fits till the 17th Aug. when I went away for my holidays; but between that date
and the 28th Aug. she had several bouts of fits which were stopped by antipyrin. In that date she was very weak but recovering and since then has had no severe run of fits although she often gets one or two a day for which she gets antipyrin. Then the above bout of fits took place she was taking Potassium Bromide regularly.

S.M., male at about 55. Suffering from Chronic Mania. He never had any epileptiform seizure till 15 June 1899. He then took three fits which succeeded each other rapidly. He was then given antipyrin 50 and took no more fits.

Jan 1900. He took 5 fits in rapid succession; at the end of the fifth he was given antipyrin 50 and had no more fits.

Oct 1899. While out walking his epileptiform fits began again and he had a bust of about fifteen before he was brought home. He was still taking them when he was given antipyrin 50; he took one other fit almost immediately after taking the antipyrin but had no others.

In this case the effect of antipyrin has always been most marked.
2.0. Female, aged 69, suffering from Epileptic Dementia; she was having a good many fits weekly; perhaps one or two two a day on the average. She was in weak health generally. She was given Antipyrine at three daily. The number of her fits decreased, but in about ten days she commenced to show signs of a general paralysis affecting particularly the arms and legs. She was taken off the Antipyrein and recovered her usual state of health. She died shortly afterwards of epilepsy.

O.O. Male, aged 20, suffering from Epileptic Mania. He was a young man of fine physique and in good health except for the Epileptic fits. He would go for some weeks without having a fit and would then suffer half a dozen or a dozen severe ones in a day or two. He took Potassium Bromide regularly and this kept his fits much in abeyance. After taking a severe fit he was always very excited and quarrelsome, this was much allayed by Antipyrein, so much so that he would come and ask for one of them draughts.

2nd April 19...

He had a severe bout of fits; he was taking them fairly rapidly. He was then given Antipyrein... had no more fits.
14 Nov. 1856. He had four fits during the day and fifteen in the night. Up to this time he had been getting Potassium Bromide 3 gr. 6 drs daily.

15 Nov. He was taking fits in the morning and got Antipyrin gr. 8 which had no effect; during the day he had 30 fits and got Antipyrin gr. 8 at night. It seemed to have little or no effect on him. During the night and up till 6 a.m. he had 80 fits and was given two doses of Potassium Bromide gr. 8. This also had no effect.

16 Nov. He was very cyanosed and collapsed; the lungs very edematous and his pulse very weak and small. Between 6 a.m. and 11 a.m. he had 60 fits and was going from one to another as fast as he could. I then injected Antipyrin gr. 4 hypodermically; after which the fits almost at once stopped till 12.30 p.m. Between which time and 1 p.m. he had four fits. I then injected another gr. 8 with some Straphanthus. He had no more fits after this till 6 p.m. when he had one fit. At that time his pulse was extremely small and weak and his lungs very edematous. He was then given Ammonia and Straphanthus regularly.

17 Nov. Had no more fits since last injection.
of Antippain and his condition was a
good deal improved. Was able to take
milk and brandy; his lungs were still
very edematous but he was not nearly so
cyanosed. He had no fits during the day.
12th Nov. He had no return of the fits and
seemed better, he was semi-conscious and
able to take brandy and milk; the condition
of his lungs was also improved. At midday
however his heart seemed to beat very
and he gradually sank and died at 10.30 p.m.

I think there can be no doubt that it was
the Antippain which stopped the fits, my
great regret in this case is that I did not
give much bigger doses at the start and
persevere with them, and that I did not
give the hypodermic injections earlier. Had
I done so I firmly believe that this case
would have recovered; it is however easy
to be wise after the fact.

R.S. Male at 32, suffering from Epileptic Frenie.
He would occasionally have a severe fit but
he frequently suffered from Petit Mal, at which
times he had a severe headache and was
irritable and quarrelsome. He would then
ask for "one of them pink draughts" which
were composed of Antippain 1/2 and
some Cardamums. This he said always cured
not only his headache but also what he called "the piddiness."

Of course I saw the drug in many other cases of epilepsy, but they were such cases that did not warrant my drawing any conclusions from them as they were cases who though having more fits than usual, were not having what I call a "bout" of fits, and I could not be reasonably sure that they would probably have had more fits if they had not taken the drug. In others too if it seemed to do little good.

Having given my list of cases I shall pass on to the second section of my thesis: viz. its action, as reported, in diseases which may have any bearing on its effect in epilepsy. Most of the matter contained in this section I have taken from a little book by Dr. Know called "Scientific Reports on Antisyphium," collected from the principal medical publications.

The references in all the cases are I believe correct.
II. Therapeutic value of Antipyrin in
Insomnia having any Barony on Epilepsy.
1. Migraine: Its beneficial action in this
is of course well known and undisputed.
Many people believe that there is a
more or less close likeness between
epilepsy and migraine, holding that
migraine is indeed an epilepsy of
certain nerves.
2. Chorea: St. Laurentin gives a case (Kre
Med. 1888 p. 11) of a girl at 7 suffering
from severe chorea. He treated her with
Antipyrin gr. xxx daily; after one week
improvement commenced; the dose
was then increased to gr. XLV and
she was completely cured in four weeks.
Mr. Ritzenfeld of Wittenberg (Ther. Monatsheft
1888, Kft 4) mentions the case of a
girl at 9 suffering from severe chorea.
An intermittent intercurrent febrile
attack caused him to prescribe Anti-
pyrin gr. St. twice daily. To his surprise
the convulsive muscular movements
became decidedly less on the day
following the commencement of this
treatment and was cured in eight
days.
Lyonnaux in the Bull. de l'Academie de
Medicine, Paris 27 Dec. 1879 gives the
following cases, A boy of 83/4 who suffered from inconstant convulsions was cured in nine days by Antipyrin. A girl of 83/4 was cured in eighteen days, another in ten days. Another girl of 10 was cured in twenty-two days, having taken 31/4 of Antipyrin in that time; and a boy of 8 was cured in eight days. He considers Antipyrin to be the most reliable and efficacious remedy in Chorea.

Dr. Wolfer (Munich med. Wochenschrift 1887) gives the case of a girl of 16 who was suffering from chorea. Bromide of Potassium Propylamine and Salicylic acid had been tried without benefit; but she was cured in twelve days by Antipyrin 25/100 twice daily.

Preval treated some cases (Kunst 1891) of laryngismus stridulus with Antipyrin grit every hour and was highly satisfied with the result.

Dr. Franz Mahnert (Mitteil. d. med. Akad. in Steierm. 1894 p. 262, 1895) says he has found it remiss the reflex irritability in cases of Paralysie agitans or laryngismus stridulus.
II. Physiological action of Antipyrin. This has not been very definitely made out, but from what literature I have read on the subject I join the following extracts.

Batten and Bobenham have investigated the physiological action of Antipyrin on the nervous system, chiefly with a view of finding the rationale of its action in migraine. According to them the drug acts on all parts of the nervous system, chiefly on the spinal cord but also on the brain and motor nerves. They say that the symptoms caused by the drug strongly resemble those of lateral sclerosis and they therefore think that it mainly affects the lateral columns of the cord; in a guinea-pig and cat it caused spastic rigidity of the hind limbs which came on whenever they tried to use them, and in all their experiments rigidity formed a marked symptom.

Lauder Brunton says it acts on the sensory nerve endings and is a local anaesthetic.

Its antipyretic action is also probably due to its action on the central nervous system. Dr. Cawth in his address to the British Medical Association says "Antipyrin was believed
by Betheilheim to cause loss of heat by its action upon the cutaneous circulation. The general blood pressure was described as falling at first but subsequently rising to a point somewhat above the normal. When the sphygmometer was applied by Van Hoorden above the arteries of subjects who had received a large dose of Antisphenin it was found by him that though the arterial pressure was not markedly influenced, the tension and tonus of the vessels were markedly increased. He also observed the sweating produced by the drug and the fall of temperature but he did not altogether unite with Betheilheim as to the manner in which this fall was produced, for after he had cut out the action of secretory cutaneous nerves by atropine he found that the fall of temperature was not arrested by suspension of diaphoresis. He pronounced therefore in favour of an action upon the seat of heat production rather than upon an increased loss of heat from the surface of the body.

Recent experiments by Savordski under the direction of B. B. in
E. Petersberg showed that the theory which supports a central action of the drug is in part, at any rate, a correct one. Sawakita recognised a rise of blood pressure equally one twentieth of the total when antipyrin was administered to dogs in the proportion of 0.3 gramme (4/5 grs) per kilogramme weight of the animals. He found that the excised heart of both mammals and amphibians contracted more strongly when small doses of the drug were added to the circulating fluid. On the other hand, perfusion of a similarly medicated fluid through the vessels of the limb caused in them a position dilatation. In the vascular system the action of the drug appeared to be chiefly upon the heart probably upon the eucto-endothelium. His thermometric observations showed him that whilst the peripheral or cutaneous temperature rose at first after antipyrin as a result of vascular dilatation, the internal temperature fell greatly. This fall occurred even when the animal was kept in a warm
chamber is enveloped in cotton-wool. In order to localise the central effect of the drug, Saunders divided the cord above the aorta and then injected antipyrin. After such a section he found that no fall of temperature was produced by the antipyrin through respiration and circulation were actively continued. Sections of the brain posterior to the corpus striatum had the same effect, but when anterior to the corpus the drug was found to preserve its action. Now the heat-regulating area described by Armstrong, Sachs, Riekel and Ott is to a large extent upon a tract located in the corpora; and assuming the correctness of the thermometric record, the conclusion seems justified that it is to a large extent upon this area or centre that the drug exerts its influence, and that its action is that of an antithermogenic.

As regards its action on the kidneys Prof. Cash says, "The action of antipyrin upon urinary secretion is marked. The nitrous urine elimination is greatly reduced, and this is not merely in conditions of disease, but it has been noted by Gabriel Lowitsch in the
case of dull as well as of feverish childern to whom Antipyrin had been given, the inorganic salts, sulphates, phosphates, etc. are markedly diminished. After the discontinuance of the drug however, all these constituents appear to be increased even relatively to the time anterior to the administration of the drug. Metabolism seems to be held in check by the Antipyrin sometimes to a remarkable extent.

Dr. Donald Macleister says, "Antipyrin increases the property of radiation from the skin, it diminishes the difference between peripheral and central temperature, it lowers the temperature as a whole, diminishing thermogenicity. It generally retards the heart's action and raises slightly the tension in the radial artery. From the stimulating action of Antipyrin in allaying pain it seems highly probable that it stimulates the inhibitory centres of nervous muscular functions, which assumption also explains its action as an antispetic.

Chappell poisoned animals with strychnia and at the same time injected Antipyrin. The convulsions which
would otherwise infallibly have occurred were prevented by Antipyrin.

P. Demme de Bon says that the administration of small but
poisonous doses to frogs and rabbits
causes alterations of the central
nervous system; first excitation
of the different centres in the
brain medulla and spinal cord
is observed followed by paralysis.
The initial excitation of the central
nervous system implicates the
muscular motor centres, and
manifests itself by general
tetanic contractions and by
increase of arterial pressure.
Subsequent paralysis is shown
by final disappearance of
reflex excitability and by
continuous decrease of arterial
pressure; although the heart's
action is not implicated.

Having mentioned the first three
sections into which I divided this
paper I now pass on to the fourth
viz., the probable mode of the action
of Antipyrin in Epilepsy and
Epileptiform convulsions.
IV Probable mode of Action of Antipyrin in Epilepsy and Epileptiform Convulsions.

There is little doubt that its effect in Epilepsy is due to its action on the central nervous system. We see that it has a direct effect on this system from the experiments of Balfour, Brodie, Snewdall, Macalister, Choppin and Demme mentioned in the last section.

The question therefore is in what part or parts of this system does it act in stopping convulsions and what is the nature of this action.

As a basis from which to make my remarks I propose adopting Huggins' Jackson's views (Lumbrian Lectures 1890) of convulsive seizures; also his division of them into three kinds and his division of the central nervous system into three levels; the three kinds of fits corresponding to the three levels.

He says "Convulsions result from excessive discharge of nerve cells, i.e., liberation of energy during
rapid decomposition (katabolism) of some matter in a part of these cells."

The three levels of the central nervous system are

1. lowest level composed of bulb, medulla oblongata.
2. middle level composed of thalamic region.
3. highest level composed of prefrontal centres.

Each level is sensory-motor and each is natural; connecting fibres run between the centres composing each level on its own side and also to the centres composing the levels of the opposite side.

The three kinds of fits are

1. Pons-bulbar (2) Epileptiform (3) Epilepsy; and they correspond to the three levels. (2) and (3) composing cortical epilepsy. They may thus be tabulated as

Pons-bulbar = lowest level fit.
Epileptiform = middle level fit
Epilepsy proper = highest level fit.

I shall also adopt his view that a convulsion starts from a discharging lesion or fulminate which may be situated in any level on either side spreading from cell to cell, from level to level and from side to side.
by means of the connecting fibres; the convulsion becoming general or remaining local according to the number of cells rendered unstable by the discharge of the original fulminate. In a convulsion therefore as regards the nervous system we may say we have three factors viz. 
1) The physiological fulminate i.e. the cells which form the actual discharging motion from which the convulsion spreads by connecting fibres to normally stable cells compelling them to join in the convulsion.
2) The connecting fibres.
3) The normal stable cells.
It is necessary therefore to decide on which of these factors Antipira acts in epilepsy and epileptiform convulsions and its mode of action on these factors or factors which it affects. I will take the connecting fibres first. It would I think be ridiculous to suppose that the drug acts on these only. That would mean that all connecting fibres in the
Three levels on both sides would be made non-conductors i.e. paralyzed by it. It would have to act on all connecting fibres in the levels generally because the position of the fulminate may be in any part of either level, and we cannot suppose that the drug would be kind enough to pick out and paralyse only those fibres connected to the cells forming the fulminate in each particular case.

If it paralysed connecting fibres generally then the same dose given to healthy people would have very different effects to what they do have; and they would show symptoms of this paralysed state of connecting fibres which they do not do.

We may then I think put aside the idea that antipyrin stops a convolution by acting on the connecting fibres.

We thus have left to decide whether the antipyrin affects the physiological fulminate or the normal stable cells which are made unstable by the fulminate, or
Dr. I think that we cannot separate them. I do not think that the drug affects the fulminate without also acting to some extent on the normal stable cells, though I do think that in fitting about a correction of the fits its action on normal stable cells is of little importance compared to its action on the overexplosive cells composing the fulminate.

In the case of X. D. when the drug was given continuously it affected all the cells generally, for it caused a general paroxysm as well as lessening the number of the fits. That is to say that it made the cells forming the fulminate more stable or rather less overexplosive, and made the normal stable cells so to speak too stable, thereby interfering with their function. We see something of the same effect when Potassium Bromide is given in too large doses for too long a time.

It is now necessary to try and decide what the nature of this action of Antipyrine in Epilepsy is.
I propose adopting the theory that the chemical composition of the cells forming the fielminate is in some way abnormal, i.e. that the cells are composed of an overexplosive substance as compared to the composition of a normal stable cell. Thus say the formula of the composition of a normal stable cell is \( X_4 Y_6 \), then the formula of the composition of cells forming the fielminate may be \( X_3 Y_9 \), which may be an overexplosive substance. If this were so then the antipyrin might act on these overexplosive cells altering their composition into the formula \( X_4 Y_6 \) i.e. that of a normal stable cell.

I think it possible that its beneficial action is mainly due to its altering in some way the chemical composition of the cells forming the fielminate, rendering them less overexplosive, and in a minor degree to its rendering the normal stable cells more stable.

As evidence too of its effect on nerve cells we have its action
also its effect on the thermicentric centre.
as given above in Chorea, Tarsypnious Stridulous, Paralytic syphus and Syphum poisoning; from its local anaesthetic action it is probable too that it acts on other parts of the nervous system, but its value in convulsions is to I think due to its action on nerve cells by lessening the liberation of energy from them generally, causing an overexplosive cell to become less so, and a normal stable cell to be more stable.

Before concluding this paper I should like to make my views on the use of Antipyrin in convulsions quite clear. I do not for a moment suggest that it can or should take the place of Potassium Bromide in the treatment of this disease. They cannot I think be compared, as they are of value, I think, in totally different cases or rather in totally different stages of a case.

A case of chronic epilepsy and its treatment may be compared to a battle; the fits are the
attacking force and the drugs are the defending one. The Potassium Bromide is the fighting line for the defenders, doing the main part of the work and keeping the enemy in check for a longer or shorter period. As a rule sooner or later, this line of defence is broken down, and the enemy comes on with a rush and captures the patient. When the enemy makes this rush, the reserves in the form of Antipyrin are brought into action, and in many cases defeats him.

After his defeat the enemy can again be held in check by the Potassium Bromide.

Let us take a supposititious case. You have a case of Chronic Epilepsy who is taking Potassium Bromide. This keeps the number of fits within reasonable bounds, it may be, for years. But at least a day comes when he takes a dozen fits; in the next twenty-four hours he has thirty, during the night he has forty; and in the morning he is dying.
from edema of the lungs, cardiac failure and general exhaustion.

Kali. The Potassium Bromide which has for years kept the fits in check is at last overcome. It is when this brief of fits begins that I
would use Antipyrin: in many cases I am sure with success.

I have too found it of great use in the excitement and
headache following Epileptic fits.

I should have liked my list of cases to have been longer, but as
the East Riding Asylum is a small one, I was restricted in the quantity
of material on which I could make observations. I hope however that
in the above paper, I have made out a case for my views, viz. that
Antipyrin is a drug of considerable value in the treatment of some
cases of Epilepsy and Epileptic Convulsions.