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CLINICAL OBSERVATIONS ON PYRODINE, A NEW ANTIPYRETIC.

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CLINICAL OBSERVATIONS ON PYRODINE, A NEW ANTIPYRETIC.

WITHIN the last few years several antipyretic medicines have come into use, notably antipyrin, antifebrin, and phenacetin. If we compare the chemical constitution and derivation of antifebrin and phenacetin, we can easily see that other bodies and substitution products can be obtained which are likely to possess temperature-reducing properties. The following observations were made on one such body, which was handed to me for examination by Dr. Liebmann, analytical chemist, of this city, which has since been registered by Messrs. Levinstein and Co. as Pyrodine, and which as its active ingredient contains acetyl-phenyl-hydrozin—$C_6H_5.N_2H_2$ (C_2H_3O).

Pyrodine is a white, crystalline powder, very sparingly soluble in cold water; it possesses very little taste and is therefore easily administered in powder form.

Before giving this drug to patients I tried it in doses of 8 and 12 grains, for several consecutive days on healthy persons, and found that it was easily taken and produced no ill effects. It caused neither nausea nor vomiting, did not interfere with digestion, and had no effect either on the body temperature or urine secretion.

Having satisfied myself that in these doses it did not produce any toxic effects, even if taken for six or eight days, I tried it on patients suffering from various forms of fever.

The first case in which I tried the drug was a case of pneumonia in a boy æt. 19. He had a rigor and vomiting on June 2nd, was admitted into the Infirmary on June 5th, with all the symptoms of croupous pneumonia of the left base. On June 6th, at 2 p.m., when the temperature was 104·2°, 9 grains of pyrodine were given and the temperature soon after fell to 99·2°, it rose after a few hours to 102° and fell again to 98·6°. There was only a slight rise after this, and the patient made a very satisfactory recovery.

The two-hourly temperature observations after the administration of the pyrodine were as follows:—

June 6th,	2 p.m.,	...temperature	104·2° (pyrodine 9 grains given).
„	4 „	„	99·2
„	6 „	„	101·2
„	8 „	„	101·4
„	10 „	„	102·0
„	12 midnight	„	101·6

June 7th,	2 a.m.	temperature	100·0
„	4 „	„	99·4
„	6 „	„	98·4
„	8 „	„	98 6
„	10 „	„	98·6
„	12 noon.....	„	99·0
„	2 p.m.	„	99·2
„	4 „	„	99·6
„	6 „	„	98·8
„	8 „	„	98·6
„	10 „	„	98·6
„	12 midnight	„	98·4

As the temperature in this case did not rise again, and as resolution set in soon after the administration of the drug, it was thought that possibly the drug had been given at the time of the crisis, and when the temperature would have fallen of its own accord.

A few days after, however, I had an opportunity of testing the antipyretic properties of pyrodine in a case of pneumonia ambulans under the care of my colleague, Dr. Morgan, who was kind enough to try the new drug.

The patient, a girl, æt. 7, had a rigor on June 9th, and was very ill for two days. On June 11th, late in the evening, she was admitted into the Infirmary, with temperature 104·1°, respirations 40, and looking very ill; the whole of the right base and middle lobe of lung showed signs of consolidation.

At midnight on the 11th, her temperature being 104·2°, she was given 4 grains of pyrodine; at 1 a.m., June 12th, temperature was 100°; there was profuse perspiration, but no nausea, vomiting, or rigor.

At 2 a.m., June 12th, temperature being 100·4°, 4 grains of pyrodine were given, and at 3 a.m. temperature was 98·2°; the temperature gradually rose, and reached 102·4° at 6 a.m., but by 9 a.m. had fallen again to 99°. Then, with few remissions, it gradually rose, and was 103·4° at 6 p.m., June 12th. The temperature then showed slight variations, but as it did not reach 104° no further antipyretic was given till 6 p.m., June 13th, when 4 grains of antifebrin were given, when the temperature fell in one hour from 103·8° to 99°. On June 16th the right base showed signs of pneumonia, and the temperature had risen to 103·9°. Three grains of antifebrin reduced the temperature in three hours to 101°, but it rose in four hours after to 104·4°. Six grains of pyrodine were now given, and the temperature fell in less than three hours to 98°, gradually rose to 103°, and fell again without further administration of the drug to 98·4°. Then it again rose, and reached 104·2° on June 18th at noon. Six grains of pyrodine sent the temperature down to 97·4° in less than three hours. The child perspired freely, but felt otherwise very comfortable. The temperature rose to 98·4° by 6 p.m. the same evening, and fell again to

96·4°, at which point it remained for some hours. This was followed by a slight rise to 98·6°, and then convalescence set in, and the child soon completely recovered.

Each fall of temperature was associated (1) with a reduction of the pulse from 10 to 20 per minute, and (2) with an increase in the quantity of urine passed. Throughout the whole of the illness the urine remained free from albumen.

The case clearly showed the powerful antipyretic properties of pyrodine, and encouraged me to try more extensive researches. This I was enabled to do at the Infirmary by the courtesy and kindness of my colleagues, who willingly allowed pyrodine to be given to cases of pyrexia under their care at the hospital; and at Monsall Fever Hospital, by the kind assistance of Dr. Oldham, Resident Medical Officer, and Mr. Edwards, the then Assistant Medical Officer, whereby I had exceptional opportunity to study the effects of pyrodine in a large number of cases of the several specific fevers.

Without entering into details, I may briefly summarise the results:

Croupous Pneumonia.—The drug was given in all cases of this affection which were admitted into the Infirmary during June, July, and August, when the temperature reached 104°. These were twelve in number. In all, pyrodine quickly reduced the temperature, and in three there was no further rise after the first administration. In the other nine the reduction lasted over 12 hours. The dose varied from 4 grains in children to 12 grains in adults. In all, it was well borne, without any unpleasant by-effects. The reduction of temperature was accompanied by profuse sweating. Eleven of the 12 cases recovered. The fatal case concerned a patient admitted under Dr. Leech, who had fallen into the river Irwell, and who was found suffering from pneumonia when admitted. He was in a moribund condition, and died nine hours after admission.

Some of the cases of pneumonia were of a very severe type, like the following, under the care of Dr. Morgan:—

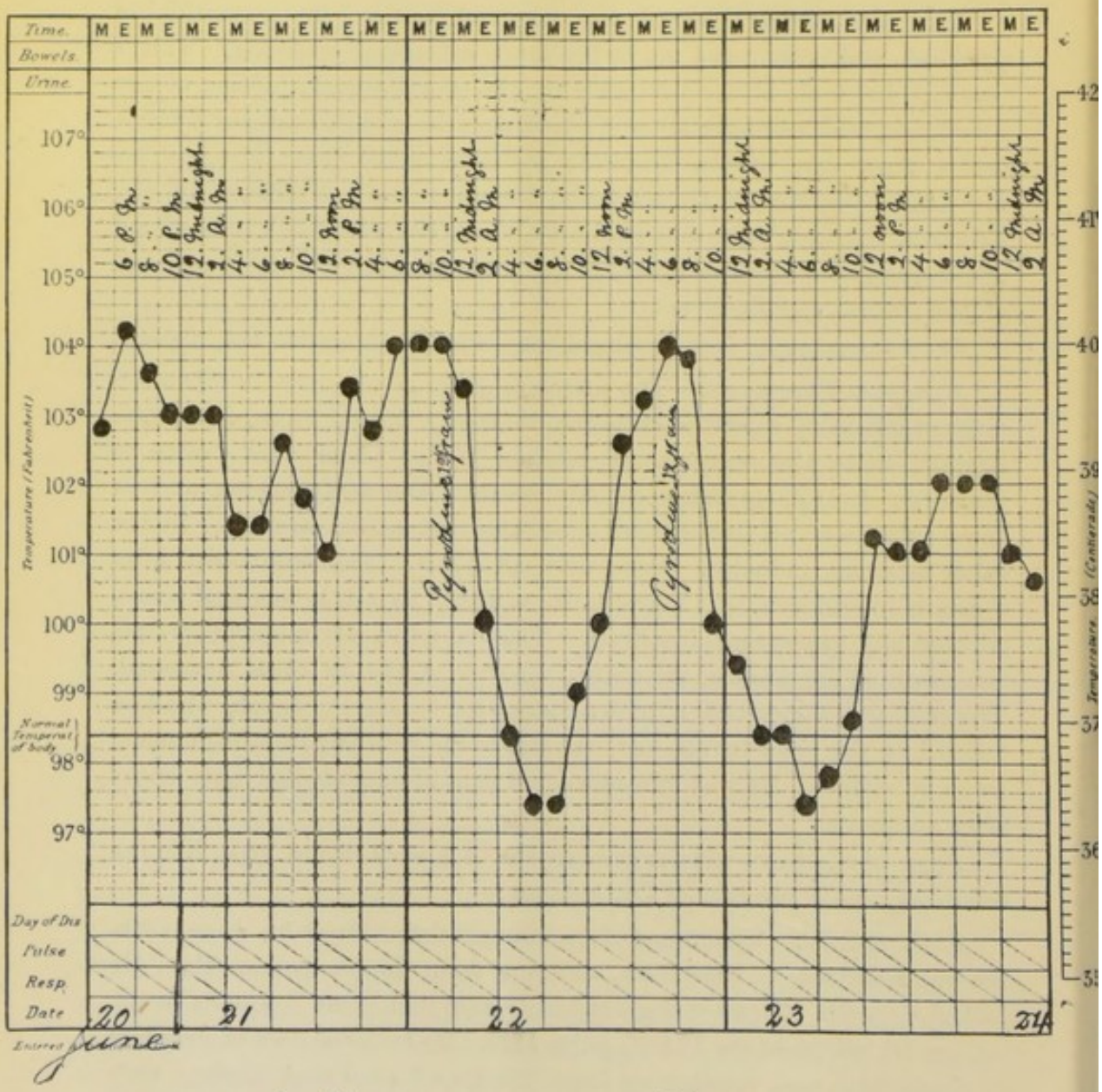
J. C., æt. 60. Symptoms of pneumonia commenced on June 13th. He was admitted on June 20th, suffering from double pneumonia. He looked very ill. There was great prostration and great dyspnœa (respirations 50, temperature 104·2°, pulse 125). He took one dose of pyrodine on June 21st, and another on June 22nd, and after that made a very satisfactory and quick recovery. The effect of pyrodine is seen on the chart on page 6.

Another case, admitted under me on July 2nd, suffered from acute nephritis, as well as from pneumonia. The pyrodine had here also a marked effect in spite of the kidney complication, and the patient left the hospital quite cured, both of the pneumonia and the nephritis.

In several cases of pneumonia where antipyrin and antifebrin had not affected the temperature, pyrodine acted at once and effectively. This was seen in two cases of pneumonia in children.

Scarlet Fever.—Pyrodine was tried in 25 cases of scarlet fever, where the initial temperature was very high, and where the children suffered very much in consequence of the high fever. The effect in these cases

Fig 1.



was very good. The temperature was quickly reduced, occasionally below normal (in one case to 95·2°), without any unpleasant symptom being produced, such as collapse or prostration. In some of these cases, where the anginal symptoms were very severe, the temperature would rise again some hours after a dose of pyrodine had been given (the dose varied from 2 to 4 grains, according to the age of the child), but was

promptly checked by a small dose of pyrodine. We did not find that the cases which had taken the drug were more liable to suffer from post-scarlatinal nephritis.

Typhus.—During June and July 20 cases of typhus were admitted into the Monsall Hospital; these cases came from a few infected houses where a small and limited epidemic had broken out. Pyrodine was given by Dr. Oldham to all these 20 cases, and the result was in every way highly satisfactory. It is well known that in typhus, more than in any other zymotic disease, the degree of pyrexia is of importance, and that in this disease most antipyretics are of little use. In former epidemics Dr. Oldham had tried kairin with very disastrous effects, quinine was found of very little service, and antipyrin only delayed the crisis. In pyrodine we found a drug which answered the purpose very well. Given in small quantities, one or two doses per diem, it reduced the temperature, and enabled the patient to pass through the fever period with a reduced temperature, varying from 100° to 102°. It produced great comfort to the patient, diminished the delirium, and did not delay the crisis. It was further found that the patients required only a very small amount of stimulants, and that their convalescence was very rapid.

Of the twenty cases treated with pyrodine, two died: a female patient, æt. 58, who was very prostrate on admission, pulse very feeble, suffering from great drowsiness and low muttering delirium, died three days after admission; and a man, æt. 39, who, when admitted, was suffering already from commencing collapse, died the second day after admission. In both these cases only one dose of pyrodine had been given.

During the month of April, ten cases of typhus were treated at Monsall Hospital without pyrodine, and of these ten cases (which, as regards gravity of disease, age, previous health, social condition of patient, could well be compared with the twenty cases of typhus treated with pyrodine) four died. In one of the twenty patients the toxic effect of the drug appeared after a few doses of pyrodine had been given, the patient became slightly jaundiced, the urine became highly coloured, and contained biliary colouring matter and globulin. These symptoms, however, rapidly passed off as soon as the drug was withheld, and were not followed by any other evil effects, except an anæmic condition of the patient, which lasted several days.

Typhoid.—We tried pyrodine in typhoid fever both at the Infirmary and at the Monsall Hospital, but we soon found that its toxic effects, which showed themselves much more readily in this disease than in any other, were a drawback to its free administration. It reduced the temperature of typhoid very effectively (in a case under the care of my colleague, Dr. Leech, where antipyrin was badly borne, pyrodine reduced the temperature eight degrees within two hours), but it was found in some cases, that after the third or fourth administration, symptoms due to

aniline poisoning (jaundice, hebetude, occasionally sickness) came on. That these symptoms were due to the action of pyrodine on the blood was shown by the experiments on animals, to be detailed hereafter. These symptoms would disappear after a few days, and be followed by anæmia, and, though not alarming in themselves, they were of sufficient intensity to make us very guarded in the administration of pyrodine in typhoid.

Pyrodine was also tried in other cases of pyrexia, as in a case of traumatic meningitis, in a case of peritonitis following acute phosphorus poisoning, and it answered well in both cases, which recovered.

In a case of *sub-acute articular rheumatism*, it produced relief from the pain, which had resisted salicylate of sodium, salol, and antipyrin, but after a few doses, toxic symptoms appeared, which were followed by somewhat prolonged anæmia.

In cases of *acute articular rheumatism*, it did not act as well as salol; I tried it, however, only in two cases.

Pyrodine in Hyperpyrexia.—From a number of cases of hyperpyrexia, especially when accompanying rheumatic arthritis, I have come to the conclusion that our antipyretic drugs, antifebrin and antipyrin, have no effect; in fact, it would appear as if the temperature increased more rapidly after their administration. This opinion is, I believe, shared by many observers. It was a matter of some interest to see whether pyrodine would act better in such cases. Unfortunately, few cases of hyperpyrexia presented themselves during the last few months. In a patient, under the care of my colleague, Mr. Heath, suffering from fracture at the base of the brain, with a temperature of 107·5°, pyrodine was tried in a large dose without much effect. Also in a case of typhoid fever, which I saw with Mr. Coates, where the temperature quickly rose from 103° to 107·8°, a small dose (3 grains) of pyrodine had but little effect. The cold bath brought the temperature down to 101°, but it quickly rose again to 107°, and the patient died. A few days ago, Dr. Oldham tried pyrodine in a case of hyperpyrexia, where the temperature was 106·5°. The temperature fell quickly, and a few hours after stood at 95·5°, the patient feeling comfortable, and this remarkable fall of eleven degrees was not associated with any symptoms of collapse. With so limited an experience, we cannot well express, as yet, an opinion as to the efficacy of pyorodine in hyperpyrexia.

Migrain.—Our experience of pyrodine in this affection is very limited. In two cases, where antipyrin failed, it acted well, and in a case of intense headache accompanying tubercular disease of the temporal bone, where quinine and antipyrin had failed to give relief, it acted well after several doses had been given, but here, too, toxic symptoms appeared.

Toxic Action of Pyrodine.—The toxic effects which pyrodine produced (jaundice, hebetude, icteric urine, which occasionally showed the presence of globulin and albumin) were so much like those seen occa-

sionally after the administration of antifebrin and phenacetin (Lépine), that it seemed likely that they were due to a mild form of hæmoglobinæmia. Experiments on animals made with pure acetylphenylhydrozin fully confirmed this view. Having obtained the necessary licence, I administered to rabbits, by means of a catheter passed into the stomach, varying doses of this body. It was found that doses of acetylphenylhydrozin, which did not exceed one grain per pound of the body weight of the animal, produced no ill effect; if, however, this dose was exceeded the animal became anæmic, and if the administration was continued for two or three days (one dose per diem), then the rabbit died from typical hæmoglobinæmia, as the post-mortem examination showed. The urine contained large quantities of hæmoglobin casts; the kidneys showed the characteristic deposits in the convoluted tubes; the spleen, of chocolate colour, contained large masses of hæmoglobin and groups of cells, each enclosing several red blood corpuscles. The liver had a peculiar ochre colour, and showed its capillaries distended with masses of hæmoglobin. The blood showed the spectrum of methæmoglobin. From these observations it is clear that pyrodine exhibits toxic effects much sooner than either antifebrin or phenacetin, and that it is not safe to give it in large doses or to repeat the dose often. The results of our investigation then briefly summed up are:—

(1) Pyrodine is a powerful anti-pyretic.

(2) It reduces fever temperatures quickly, and maintains the temperature at a low level for some hours.

(3) It is easily taken, and produces marked perspiration, but not nausea, vomiting, or collapse.

(4) It is especially applicable in cases of pneumonia, scarlet fever, and typhus. Given in small doses in the latter disease it enables the patient to pass through the fever period at a lower temperature range without delaying the crisis, and it seems also to shorten the period of convalescence.

(5) It is less applicable in cases of typhoid, owing to the early exhibition of toxic symptoms.

(6) It appears to act equally well in migrain and neuralgia, though on this point our observations are as yet not numerous enough to admit of a definite opinion.

(7) Given in often repeated doses at short intervals, it easily shows toxic properties and these depend on the action of the drug on the blood, producing hæmoglobinæmia. It should not be given (unless the temperature be very high) oftener than once in 18 or 24 hours, and it is not safe to continue its use for more than a few days.

(8) It is found to act in cases where the other antipyretics have failed.

(9) The dose for children is 2 to 4 grains; for adults, 8 to 12 grains.

(10) It is a much more powerful antipyretic than either antipyrin, antifebrin, or phenacetin, but it is also much more toxic than these bodies. This disadvantage is, however, reduced by the fact that it is rarely necessary to give more than one dose in 12 to 18 hours, as the temperature is kept low for a longer period than if any of the other antipyretics are given.

(11) It reduces the pulse as well as the temperature, and often causes diuresis.

From experiments made by Dr. R. Wild, assistant to Dr. Leech in the pharmacological laboratory of the Owens College, it appears that pyrodine has no effect on voluntary muscle and but little on the isolated heart of the frog. It causes dilatation of the blood vessels, but it does so by acting on the spinal cord and not on the vessels directly, and it also has a paralysing action on the central nervous system. (Dr. Wild's report is appended.)

While engaged in these observations my attention was drawn to a communication published by Nicot (*Nouv. Remèdes*, 1887, 102) and reviewed in the *Pharmaceutische Zeitung*, March 19, 1887, where a combination of laevulinic acid and phenylhydrozin, under the name of antithermin, is described as possessing antipyretic properties. According to the notice in the *Pharmaceutische Zeitung* (the original was not accessible to me) nothing is said about the dose, mode of administration, or clinical experience, and I have not been able to find any further notice of this body.

My intention in this short communication is simply to record the clinical experiences on the temperature-reducing properties of this new body; how far the different antipyretics are useful in fever is a much wider question, which I do not attempt to discuss. Apart from the therapeutic aspect, it is of scientific interest to know that there is a series of bodies which act as powerful antipyretics. The list of bodies will probably be still further enlarged, and it must be our object to find one which, while acting as a temperature-reducing agent, exhibits the least toxic effects. Further and more extended observations will probably also show, that though these bodies have a similar action, yet they are not all equally applicable to all forms of fevers.

Report of Dr. R. Wild on the Action of Pyrodine on the Frog and Terrapin.

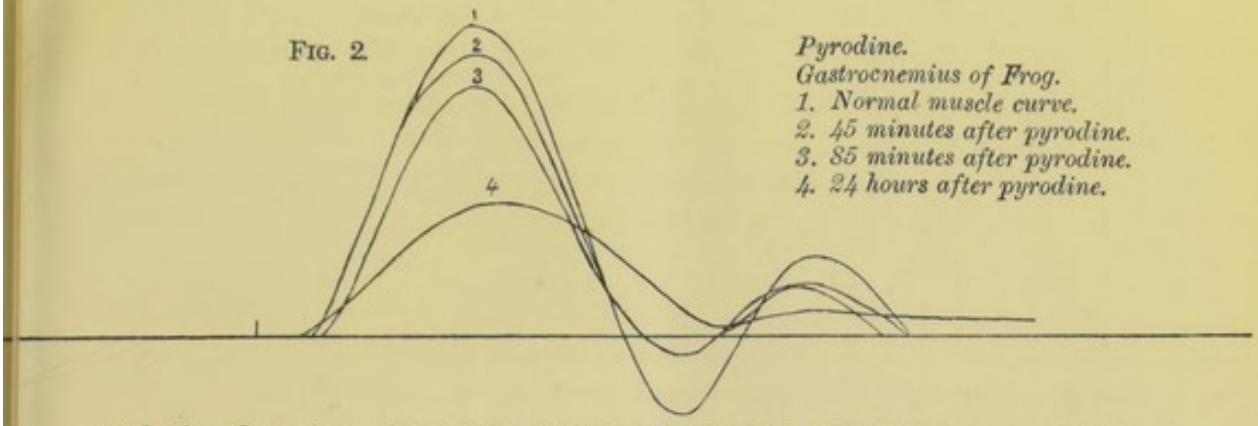
I performed a number of experiments with pyrodine in the Pharmacological Laboratory of the Owens College, in order to ascertain what action the drug possessed upon the tissues themselves. A summary of the results obtained shows :—

(1) *On Voluntary Muscle.*—Pyrodine has very little effect upon muscular tissue; the gastrocnemius of the frog was arranged to record

contractions on a smoked cylinder while soaking in a saline solution containing 1-1,000 of pyrodine. The tracings given above show that after 24 hours' action of the drug the muscle was capable of giving a fairly good contraction. (See Fig. 2.)

(2) *On the Isolated Heart of the Frog* arranged in "Roy's" apparatus, "Ringer's Saline Solution" being used as the circulating fluid. After the circulation for 35 seconds of saline containing 1-1,000 of pyrodine the heart beats were slightly quickened, the height of contraction lowered,

FIG. 2.



and the duration of systole shortened, diastole not being appreciably affected; the heart was only killed by the drug after it had acted for a prolonged period. Thus pyrodine is not an active cardiac poison, though strong solutions (1-1,000) depress the heart's action and lessen the strength of each individual contraction—comparing with the effect on voluntary muscle (supra) in which the height of contraction was diminished, but the muscle was not killed by the drug. (See Fig 3.)

(3) *On the Vessels.*—The terrapin was used to determine this effect

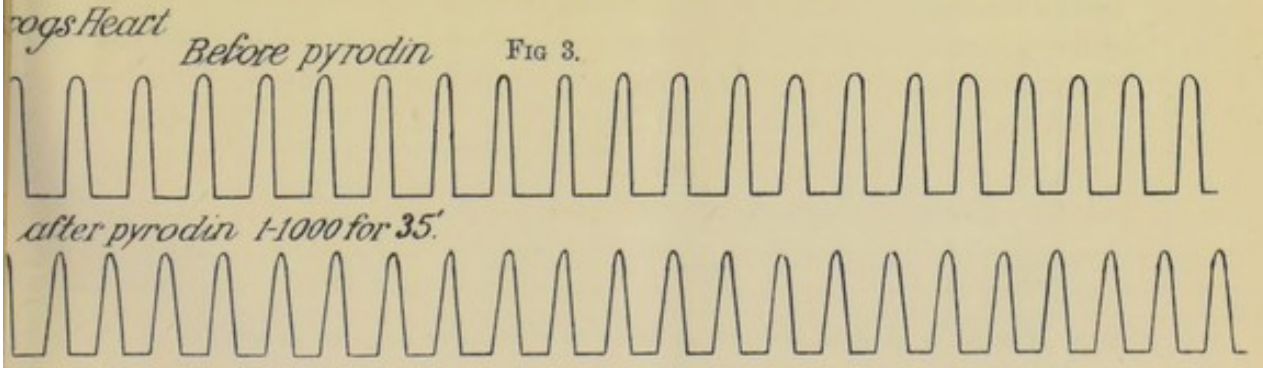


FIG 3.

after decapitation; a cannula connected with a reservoir of saline solution was placed in the left thoracic aorta, the other five aortæ ligatured and the heart removed, the outflow from the veins being measured every five minutes, and the pressure of the saline solution in the reservoir kept constant. At a given time saline solution containing pyrodine was substituted for pure saline.

Dilatation of the vessels—shown by the increased flow—occurred with solutions containing 1-10,000 of pyrodine; also with 1-5,000 and

1-1,000, provided that the spinal cord was intact; after destruction of the spinal cord no dilatation of the vessels was produced by the drug, showing that pyrodine had no action on the vascular walls themselves. As a proof that non-dilatation of the vessels after destruction of the cord was not due to death of the animal, or to anything wrong with the apparatus, a solution of sodium nitrite 1-1,000 (which is known to act upon the vessels directly) was circulated, and dilatation of the vessels took place. (See Fig. 4.)

FIG 4.

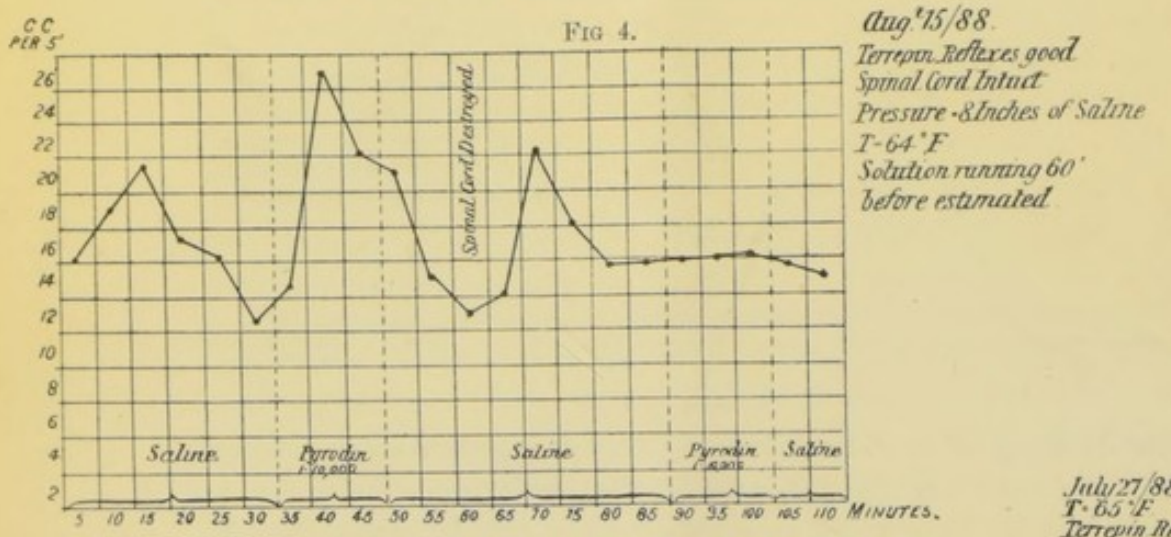
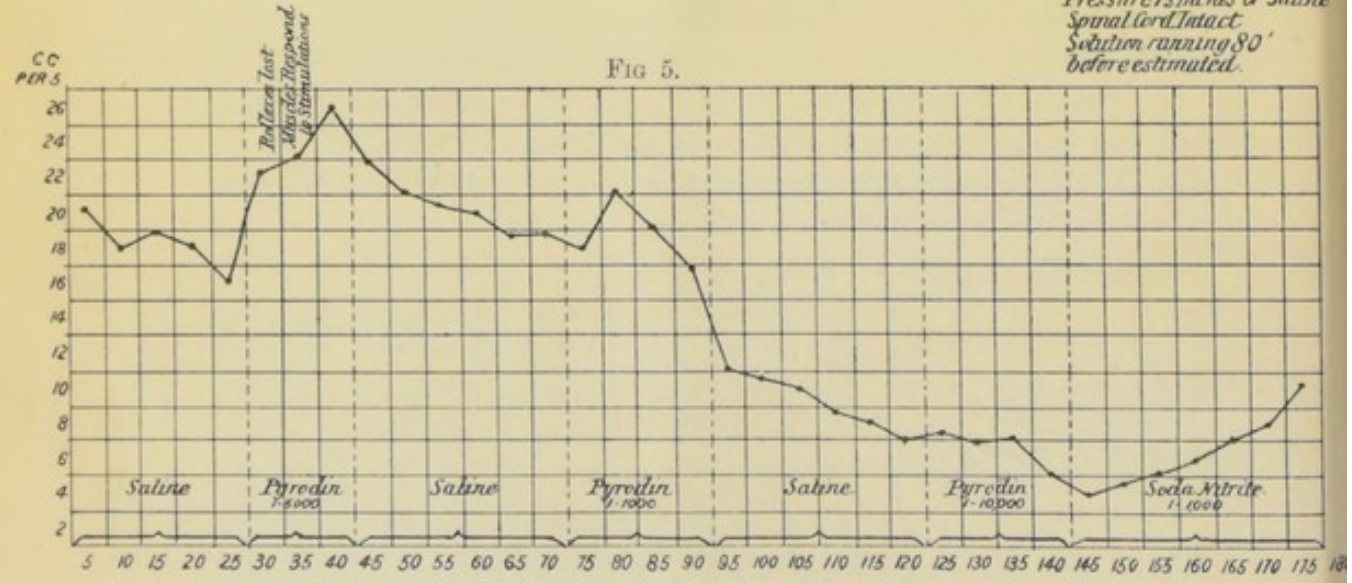


FIG 5.



(4) *On the Spinal Cord.*—Pyrodine dilates the vessels by acting on the centres in the spinal cord. It has also a paralysing action on the central nervous system, as after fifteen minutes' circulation of 1-5,000 solution all reflex action ceased, no movements being obtained by external stimulation—normal contractions of the muscles being obtainable by direct stimulation of the muscles or motor nerves. (See Fig. 5.)

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