## EXOPETEADMID GOIDER

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with special reference to its treatment by Thyrus Cland.

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The deformity present in Exophthalmic Goitre, the gravity of the symptoms generally, and the frequency of its occurrence combine to render the treatment of this disease a subject of great importance and deep interest to medical men, - an importance and an interest which are increased rather than diminished by the obscurity surrounding the actiology of this distressing disease. In the course of this paper I will first briefly notice the history of the disease and some of the main theories as to its causation. It will be shown that while earlier theories as to the nature of Exophthalmic Goitre, for the most part account for a certain symptom or group of symptoms none of them in themselves are sufficient to embrace the widespread disturbance of the astabolish of the body. Nodern investigations, consideration of which has led me to adopt the treatment, the striking results of which I shall describe later, have suggested that for a cause we will have rather to look to the higher nerve centres than to one special branch of the I shall refer in due course to ascertained nervous or other system. facts in the previous history of certain cases that seem strongly to support some such view, and as a result it may be necessary to alter our view of what we shall classify as primary and what as secondary symptoms. Since the publication of Graves<sup>•</sup> Clinical Lectures in 1848 the association of Exophthalmos, with palpitation of the heart and hypertrophy of the thyroid gland, has come to be recognised as constituting a In this country and in France it is usually called specific disease.

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Trousseau notices various other names such as "Graves Disease". "Exophthalmic Goitre", "Exophthalmic Cachexia", "Cacheotic Exophthalmus". and "Basedow's Disease". By the last of these names it is usually known in Germany, for as early as 1848 Basedow had published an article in Caspers Mochenschrift and given it the mane of Clotzergen Cachezie. For at least a century and a half the disease under some of its forms had claimed the attention of physicians if we may consider a reference by St. Yves<sup>2</sup> to Exophthalmos to bear upon it. At Lyons and Rome about the end of the eighteenth century Gilibert and Flajani had both observed cases of goitre, the latter particularly noticing its association with palpitation of the heart and even refers to an exophthal -nic condition in detailing certain cases. In this country a succession of observers, commencing with Parry at Bath about 1800, have written on this disease, but for the first clear delineation of the three main symptoms we are indebted to Graves. Influenced apparently by the communication from Stokes, which he afterwards published in his clinical lectures he firally associated exceptualmos with the other symptoms.

goitre, with mere incidental notice of exophthalmoni

1 Trousseau's Clinical Medicine Vol.1 p.548. New Sydenham Society 1888. 2 Nouveau Traite des Maladies des Yeax. Paris 1782.

though prior to this he inclined to lay more stress on palpitation and

3 Guiseppe Flajani, Collez. D'Osservaz. e Refless.di Chirurgia. Rome 1803. 4. Geleb Hillier Parry, Collections from the unpublished writings.

London. 1825.

A few years later than Graves in Dublin Begbie<sup>5</sup> in Scotland about 1839 was beginning to direct his attention to the same group of symptoms. On the continent Basedow, Birsch, Demours, Desmarres, Mackenzie etc., were all contributing in their several ways to a completer series of observations on the symptomatology of the subject. In German medical circles to Basedow is given the credit of first observing the associated group of symptons which we now recognize as that of ""wopthal do Coites" to have already each dest descal public ward three symptoms as characteristic of the disease, viz: - palpitation, hypertrophy of thyroid gland, and protrusion of the eyeballs. These with the rythnical vibratory tremors, and pulsation of the whole neck - especially on its lateral portions and in the region of the thyroid - are usually classified to prictury, while as secondary symptoms are classified the other functional disturbances such as those of the digestive, respiratory Indeed the wide nervous, generative, integunentary and other systems. range of possible systematic disturbance may be said to be characteristi of the diamon, and has to be carefully noted in investigating its origin Although in a typical case the primary symptoms are all present, usually in the order given, we may have otherwise well marked cases in which for a long time one or other may be absent. Such have usually been con--sidered incomplete. Our view, however, of what constitutes a complete case will be to some extent affected by the theory we adopt.

5 Contributions to Practical Nedicine. Begbie, Edinburgh, 1868,

In many cases the exciting cause of the appearance of Exepthalnic Goitre can be traced to sudden fright. prolonged and intense emotion or mental andiety, particularly at certain critical ages such as at puberty, - especially in females, - exhausted conditions of the system as in Anaemia, or exhaustion after severe illness. In accordance with this the period in which the disease most frequently develops is .in females from the ages of 15 to 30, and in males from 30 to 45. Withuisen noted that in 50 cases only 8 occurred in males. The radical changes of the system in females at the age of puberty doubtless have some bearing on this fact, diminishing the power of resistance to such exciting causes. The observation of this connection has doubtless led to the various theories postulating an anaemic origin. A theory of this kind was advanced as early as 1839 by Begbie, but has of late been abandoned for as Sattler shows the disease is found to attack persons in robust health. I would suggest that the Anaemia may be the result of the general secretory derengement which we will see accompanies Exercitativis Soutre. At any rate a relationship of the spleen and lymphoid structures in blood making is suggested by a case of Palmas<sup>8</sup> diagnosced as Hodgkins disease, in which a condition of the blood similar to leukaemia afterwards developed, and at the necropsy

6 Trousseau's Clinical Medicine Vol.1 p.552. New Sydenkam Society 1868. 7 Graefe Saemisck Archives, Leipzig 1880.

8 British Vedical Journal. p.1635. December 5tk. 1896.

a primary round celled **m**arcoma of the thymus was revealed. Further evidence of some such relationship of function in the different clands is furnished by the interchangeability between the spleen and other lymphoid structures in Hodgkins disease. We will have later on reason to connect with those lymphoid structures the Thymus and that Horsley calls the parathyroid gland. A cause has also been sought for in the derangement of the sexual functions, and it was noticed by Trousseau that Amenorrhoea frequently accompanied Exophthalmic Soitre. As Amenorrhoea is a result of Anaemia we can scarcely consider it in any sense a cause, though there is an observable relation between increased activity of thyroid and active changes in the sexual system. In my cases I noted that an increase of the thyroid swelling and Ex--ophthalmos corresponded with the menstrual period. A suggestion was thrown out by Charcot that the origin may be of a psychical kind, and he indicates the possibility of the sympathetic system being chiefly involved. That this is so a group of the symptoms may be taken to prove. We have, for instance in many cases a rise of temperature, sweatings, excessive and persistent diarrhoea, watery stools etc.; which are evidence of sympathetic disturbance, and a great deal of recent work has been devoted to tracing the connection of the three main symptoms to the same cause. In this connection we cannot but refer to Claud Bernard's carefully conducted experiments. which have shown that the oculo-pupillary and vaso-thermic centres are

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9 Britick Medical Journal. December 5th. 1896 Borsley. 10 Lecons sur le Système. Claud Bernard.

at different levels in the cord, and that dilatation of the vessels and vaso-thermic effects follow from section of ascending cord of 11 thoracic sympathetic. Following out Bernard's experiments Aran suggested exophalmos might be due to icritition of the cervical sympathetic, through spasm in the musculus orbitalis of Muller. Undue retraction of the upper evelid called Stellwags sign is probably due to this cause, but we may doubt if a muscle so little developed in man could produce exopthalmos, and it seems a more satisfactory view to suppose it due to the engorgement of the post-orbital vessels. The further eye symptom called Von Graefe's which is present in well marked cases, and consists of want of co-ordination of the movements of the eyeball and eyelid, also suggest paralysis of Some kind. Ne have here two sets of effects, due respectively to paralysis and irritation of different fibres of sympathetic system. So far, therefore, as the symptoms due to sympathetic disturbance dealt with in these experiments go, we have in the first place the opposite condition of paralysis on the one hand and irritation on the other to account for. But as Mr Horaley points out "it is very difficult to understand how such a theory as that of the influence of the sympathetic nerve and its supposed ability to produce constitutional disease can ever have found a serious position in medical literature and work".

11 'Aran Bulletin de Academia de Vedi**cint. 1860.** 

Besides it is necessary to assume a condition of irritation in certain sympathetic fibres persisting for a length of time of which we have no analogous experience, as the symptoms referred to generally persist Koeben has remarked the connection between pressure of for years. enlarged thyroid on cervical sympathetic and the symptoms of the disease. but it is sufficient to point out that enlargement by no means un--iformly precedes the other symptoms, nor do the eye and heart symptoms 13 always appear where we have the enlargement of thyroid. Benedikt and Friedrich<sup>14</sup> have come to diametrically opposite conclusions as to the kind of sympathetic condition involved, the same symptoms being attributed by the former to irritation, which by the latter are con--sidered to be due to paralysis. An attempt has been made by Geigel to correlate these opposite effects, by transferring the point of origin to the centres described by Bernard. These centres are however so closely related, that the problem of a common letion acting so different--ly on them, is not easier of solution than that involved in amsuming a different effect on the fibres of the sympathetic itself, and it is this difficulty that forms the basis of Eulenburg's criticism of the hy--pothesis. That the agency of the vaso-motor system is involved

12 Koeben De Exopthalmos de Struma cum Gordis Affectione. Berlin 1855. 13 Benedikt. Viener Med. Presse. 1869.

14 Friedrich Krankheiten des Herzens Erlangen; 1867.

15 Geigel. Murzburg. Med. Wochenschrift 1866

in producing the symptoms, is of course chearly evident, but the con--flict of opinion on the way in which this agency is brought into effect. serves to make us look for a more central cause them the immediate environment of the sympathetic nerves. In this respect Charcot's suggestion of a psychical origin, if we may assume him to have meant by this some of the higher centres of intellection, is worthy of careful consideration, supported as it is by numerous cases in which mental shock of some kind is traceable in the previous history. We need only refer briefly to such other causes as Neurosis of Heart advocated by 10 Stokes and Neurosis by Graves. In both cases the effects seem much nore widespread than the cause can satisfactory explain. Modern research, regarding this disease, has turned mainly on the discovery of the secretary functions of the ductless glands, the importance of which in the bodily economy was until recent times scarcely considered The experiments of Schiff. Gley. Boffmeister. V. Biselberg. Sand. at all. -stron, Kohn, Edmonds and Horsley, 9 have mainly contributed to the know--ledge of these bodies which we now possess. The results they have established we may briefly summarise. In the first place the thyroid has been definitely ascertained to exercise secretory functions of great importance, related probably to a separate function of the

18 Diseases of Heart and Aorta. Dublin 1354. 17 Spaves Clinical Lectures Dublin 1848.

parathyroid which is now considered a gland sui generis. That the thyroid is important to life was shown by the experiments of Schiff on Carnivora, and these experiments were continued and brought to bear more directly on conditions in the human system, by Horsley's experiments on monkeys and herbiverous animals. He subbled din leave--strating the minilarity of the symptoms following on thyroidectomy to those of myxcedema. Microscopic investigations have still further confirmed this discovery, by tracing the changes in the structure of the gland in artificially produced hypertrophy, and in enlargement of the gland from natural causes. In parenchymatous goitres it has been shown that the changes in the epithelium and acini, are similar to the changes that take place in hypertrophy, and in Exophthalmic Goitre there is still further analogy to the hypertrephic condition, in respect of changes in the colloidal material, which become watery, the solid condents of the acini being represented by a granular debris, the gland synchronously becoming enlarged just as in hypertrophy. Another set of observations have been directed to the other ductless glands, and practically a new set of relations suggested between the thyroid, parathyroid, thymus and other lymphoid structures in the body. A fact most important in view of our subject is the frequent hypertrophy of the 18 thymus, spleen, and lymphoid structures of neck, observable in this disease.

18 Nedical Record. 1885. Vol. 1 p.743.

According to Joffroy<sup>19</sup> revival of thymus occurs only in this disease, and it is also important to note that the disease is most common at the period of adolesence, when the thymus normally disappears. This hypertrophy we will have to notice later as possibly of a compensatory nature. These facts are in themselves sufficiently striking and seemed to me to have such deep significance, that in the autumn of 1896, having been interested in a case of **Exeptthelmic Soitre, I resolved to try the** administration of thymus gland tabloids and to note accurately the results obtained.

## Case 1.

About two years ago I was called to see Wrs **E.**, act. 33 residing at Cowdenbeath. She complained principally of protrusion of the eyeballs, palpitation and general weakness, with occasional attacks of severe headache. Her appetite was good, but she was subject to attacks of diarrhoea. Her father and mother are both alive and well, and out of a family of seven, there are two dead. A brother died at the age of 19 from what was called brain fever, a sister died at the ohange of life. All the rest are healthy except patient herself.

19 Joffroy. a Progres. Ned. 1894 Vol. . p. ^8.

Previous History: - She was up till five years ago in good health. About that time she was confined, and a fortnight after her confinement one of her children took seriously ill. The doctor who was attending her told her the child would not recover. The shock of this announce--ment had such a deleterious effect. that she was confined to bed for four months. Since that shock she has never been the same and has at times suffered from breathlessness, but the first thing that drew her attention was palpitation, which was worse in the mornings and aggra--vated by the least excitement or exertion. It was not till two years ago that she noticed a swelling in her neck. This increased in size but generally speaking there was no pain except that at times she felt a choking sensation. The palpitation at this period became worse and nore constant and her eyes more prominent. Her menstruation began at 15 and was quite regular. She has had five of a family and all are alive and healthy. Her condition presented to me a well marked case of Exephthalmic Geitre, and I commensed my treatment by prescribing Digitalis the result of which was unsatisfactory. In this case I also used Belladonna, Iron, and Browides, but she obtained from them no more than a slight temporary benefit. I then ordered her away for a holiday, and it was not till October 27th. 1896 that I saw her again. She said she was no better, and in fact from her appearance, being greatly enaciated and suffering greatly from trenors of the hand, she was evidently nuch worse. The protrusion of her eyes was more prosentiesd, and Ven Graefe's sign was marked. Her husband remarked to me that during along her eyes were half open, and she often walked in her sleep.

Temperature 99. Respiration 25. Pulse, after sevenal minutes rest, was 140. The greatest circumference of neck taken just above the vertebra prominens measured 14 inches. The swelling of the gland was elastic, and on placing the hand over it a distinct thrill could be detected. A blowing nurmur was also heard over it. There was well marked pulsation in the vessels of the neck. Inspection of the chest revealed undue pulsation over the cardiac area, the greatest pulsation being in the fifth space, 1<sup>1</sup> inches within the nipple line. Cardiac dulness normal, and owing to the violent pulsation over it, no definite murnur could be detected, either at base or apex. Lungs normal. Vocal resonance and fremitus equal on both sides, and there was no rales. Liver and spleen normal. Urine - amber colour and no trace of albumen or agar. As she was getting worse I was led to try the effect of thymus gland. Before, however, commencing the treatment I had her photograph and weight taken, and obtained a sphygnographic tracing of her pulse. I have hepeated the sphygnographic observations at intervals and illustrate this paper with a few of these. In a chart appended, I will show the daily quantities of Thymus administered, the pulse rate and temperature. I will also give a table showing body weight taken at intervals of about a In this case I produce also a photograph taken a few days ago, month. The treatment commenced on October 30th. when I administered 30 grains of thynus gland tabloids, - (Burroughs Wellcome & Co.). - which are prepared by drying the fresh gland of sheep at a low temperature, by means of a current of air in a special manner, - thus reduced to powder it I began with a dose of 30 grains of the tabloids which is compressed. I gradually increased to 105 grains on the thirteenth day of treatment.

The pulse had by that time been reduced from 146 to 104. The inpulse over the cardiac area was diminished, and tremors which were at the beginning well marked were now much less noticeable. Patient feeling better according to her own account, and less excitable.. At this point vomiting occurred after taking the tabloids, and I thereupon reduced the A slight increase in pulse rate supervened. On the sixteenth dose. day I again increased the dose to 105 grains. On the 15th. November (seventeenth day) pulse 100. On 30th. November one month after commencement of treatment pulse rate fell below 100 and tremors of hand were from this time completely gone. The low pulse rate continued until December 23rd. with the exception of one day (December 2nd.) when a second attack of vomiting occurred. I consequently reduced the dose from 150 to 75 grains. On 23rd. December a slight attack of Tonsillitis set in which passed off in a day or two. During this time no tabloids were given owing to her inability to swallow. The goitre was at this date perceptibly diminished, exceptions less marked, palpitation practice--sally gone, and the thrill over the thyroid less marked. From February 1st. she has been taking 60 grains daily. There was no recurrence of palpitation, but a slight urticaria appeared on the skin, which in a fortnight or so disappeared. Measurement of neck at this date was 12? inches. For some time the patient had confined herself to the house pretty much, through sensitiveness to the peouliarity of her appearance, but from this date she considered her appearance so much improved that she resumed going out. The main improvement was a gain of flesh, which by this time was very marked. Her weight had increased to 8 stones 2 lbs. From this time there was no interruption to the steady improvement

indicated on chart by pulse rate. There was a gradual diminution of thyroid swelling until on May 20th., when last photograph was taken, the gland had fallen to normal size. **The Exephth**almos still persists to some small extent, although she has less feeling of stiffness in closing the eyes. The case is noticeable for the rapid reduction of pulse rate under administration of large doses of this drug when other drugs appeared inefficient to produce this effect.

## Case 2.

About two years age I was called to a Mrs H. aet. 47 residing also in this district, who complained of great weakness, palpitation, and a swelling in her neck. On making enquiry into her condition she made known to me the following facts. She had no inclination for food, often she had severe attacks of diarrhoea, but when not troubled with it was rather inclined to be costive. A very noticeable feature in her case was profuse sweatings of which she complained, and which imparted to her skin a sort of greasy look. She was often thirsty and sometimes vomited. Her father and mother were both dead the former at 56 years of age from Inflammation of the Lungs, the latter at 74, cause unknown. Of a family of seven all were alive and healthy except one sister, who died at the age of 50 from Dropsy. Enquiry into her own previous history shows that she had been in good health up to three years ago and in fact never had any serious trouble before that time. She was then residing in Dunfermline and in the month of November 1894 two months before her last confinement, she got a great fright during the night, owing to the bursting

of the water pipes which were situated over the bed. She has from that time never been well and she attributes her present trouble to that gir--cunstance. It was a fortnight before she was able to leave her bed after her confinement owing to weakness. Innediately after this she had frequent attacks of palpitation, and while dressing one day she was attracted by a swelling in her neck. She came forward to her husband and said "John, I wonder what that is that's growing there?". Her husband then sent for me. On examination of the patient I found her in an anaemic and emaciated condition, with slight tremors in her hands. One point was noticeable and that was there was scarcely any prominence of her eyeballs, but beyond this fast she had the well marked symptoms of Breakthalmic Goitre. I prescribed Finct. Digitalis 10 m. doses three times a day but she had to stop it as it did not control the palpitation and was setting up stomach symptoms. I then ordered her Oppenheimer's Bi- palatimoids which contain Iron and Arsenic, but I was sadly dis--appointed in the results obtained. After this she went a long holiday to see if the change of air would do her good. I was called to see her on the 39th. March last when she said she was no bester. On making a closer examination of her condition it may be mentioned that now there was well marked exepthalmos, but deither Von Graefe's nor Stellwag's signs could be eligited. There was a great enlargement of the thyroid, the greatest circumference of neck measured 15t inches. The blood vehicles could be seen pulsating at the sides of the tumour, and by placing the hand over it one felt a distinct thrill. On auscultation there was a loud bruit heard over it. On examination of chest there was undue pulsation over the cardiac area, the greatest pulsation being detected

in the sixth space 1<sup>1</sup>/<sub>2</sub> inches within the nipple line. Area of cardiac dulness normal and no murnur could be heard over it. There was also pulsation in epigastrium. On examination of the lungs beyond a few rales there was nothing abnormal. Liver and Spleen normal. Urine normal. Owing to the splendid mesults I was obtaining in Case No. 1 I did not scruple in ordering at once thymus tabloids, and in this case also I endeavoured to watch the effects carefully. Before counenoing the treatment with the gland I had her weight taken also a photograph and sphygnographic tracing of pulse. The treatment connenced on March 24th. when I administered 30 grains which I gradually increased to 75 on April 6th. The pulse had by this time been reduced from 130 to 98. The pulsation in the vessels of the neck and also the cardiac impulse were greatly diminished. The tremors which were slight to commence with had The improvement went steadily on during several entirely disappeared. Pulse rate fell rapidly as shown in the Chart. Measurement weeks. of neck fell from 157 to 137 inches. On April 29th. thrill was extremely slight, and exochthalmost less marked. Patient's generations also indicated improvement, the languid feeling at night of which she complained at beginning of treatment had disappeared, and her general health was greatly She took her food better and her bowels acted more regularly. inproved. On May 6th. she took a rigor, distressing dyspnoea supervened, her pulse sese to 130. Temperature 102.5. She gradually became worse with all the symptoms of Pneumonia, the pulse became very small and irregular, and on 11th. May(the sigth day) she died from failure of the heart's action. The unfortunate prejudice against post-mortem examinations prevented ne obtaining one in this case.

IN both cases detailed the rapid reduction of tremors was a notice--able feature and the immediate control of the heart's action obtained was scarcely less marked. The remaining characteristic symptoms yielded more slowly but the results here were exceedingly striking when contrasted with the results I had seen in treatment with other drugs. In short, I am so firmly convinced that in Thymus we possess a therapeutic agent of the highest value in the treatment of this disease, that the physician may with the greatest confidence look for rapid and satisfactory results.

It is evident that the striking results following the administra--tion of Thymus in this disease must lead to a reconsideration of the whole faots, such as that which followed Dr George Murray's brilliant success in treatment of Myxoedema by "administration of that structure the less of which had caused the disease"<sup>20</sup>. One point cannot be over--emphasied, that we are dealing with a disease which causes a grave and complex disturbance of the metabolism of the body. The results of thyroidectomy experiments sufficiently prove that athyroidism can produce large effects of this nature, and the faots further seem to indicate that hyperthyroidism may have equally detrimental results. There is of course a difficulty in proving whether in **Rephthalmie Ceitre** we have to do with a hyperactivity of thyroid or a perversion of the secretion. In either case, however, if we may assume that in the normal

20 Beritagy. British Medical Journal December 5th. 1896.

condition there is a certain balance maintained between the different ductless glands, and if the normal thyroid is called upon to produce in certain quantity a chemical element necessary to the economy of the body. then it is apparent that a disturban de of either the quality or amount of this secretion might equally produce detrimental results. Now it is in the direction of chemical changes in the composition of the secretions of these glands that the facts seen to me to point. There is even evidence that on the thyroid depends the main tenance of the balance against the secretions of the whole series of lymphoid structures, excess or defect of either element forming what for the wants of a better analogy we may call a toxic, but of different chemical characters. As we should expect. we find that splenic extract has been substituted for thymus in treatment of Graves disease with beneficial results.<sup>21</sup> As suggesting the opposition referred to, the different curve of blood pressure produced by thyroid and splenic extracts may be cited. We may assume still further that the duties of the thysus on its disappedrance are taken up by some other organ, or in view of the increased activity of thyroid at this period, it may be that a changed proportion of the elements in the secretion is adjusted to the changed requirements of the body, in respect for example of greater cerebral activity etc.

21 Professor Wood. Am. Journal Med. Sc. June 1898 28 Dr George Aliver. Groomian Lestures. 1993.

The unwieldy condition of the mind, the languid state of thought end volition in Myxoedema, and the high-strung nervous temperament in Emephthelmic Goitre show some stimulating influence of thyroid on certain cerebral centres. The frequency of mental shock or emotional disturbance in previous history of the disease under consideration, also indicates an origin in the higher centres. My conclusion is that from an origin in the higher centres, we get, transmitted in some way, an influence which throws out of gear as it were, some of the ductless glands, either through excess or defect of their secretions disturbing the balance of their chemical contributions to the blood. This, it seems to me, is the only hypothesis on which we can adequately account for the various symptoms of disturbance in pany different systems of the body. Case 1. Mrs R.

	Body Weight		
1896	Stns.	lbs.	
October 28.	7	8	(before treatment)
December 1	7	61	
1897			
January 4	7	<u>1</u> 2	
February 1	Ċ.	2	
March 1	R	41	
April 3	3	7	
May 3	8	9	· ·
1ay 30	8	10	

From connencement of treatment to May 20th. there has been a gradual increase in weight. She has gained 1stn. 81bs.

Measurements of circumference of Neck.

1896		Inches	
Oc <b>to</b> ber	28	14	
December	r 1	13 <del>1</del>	
1897			
February	1	127	
April	<u> </u>	111	
Map	20	113	



Pulse Tracings. Pressure about 3oz.

-25



Pulse fracings. Pressure about 3oz.

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## 1897.









N.B. Pulse, taken after several minutes rest. .

reneren



Pulse taken after Several minutes rest. NR.

interested