could be more accurately attained by adopting some modification of Kjeldahl's process, but I wished to ascertain the action of the drugs used on the excretion of urea and uric acid. Unfortunately, the urine was frequently either neutral or faintly acid, so that conclusions drawn from the results obtained would probably be fallacious. Various expedients were tried to prevent its decomposition, but without much success. The quantity of urine was above the average—about 2,000 c.cm., and the specific gravity rarely exceeded 1010. The colour, considering the quantity, appeared to be normal. Although it was examined repeatedly for albumen no trace was detected.

For the estimation of urea Hufner's hypobromite method was employed. For estimating uric acid Hopkins's long process was used until January 7th, when I tried Otto Folin's modification of Hopkins's short method. This consists essentially in substituting 10 g. of ammonium sulphate for saturation with ammonium chloride in 100 c.cm. of urine, and subsequently washing the precipitate with a 10 per cent. solution of ammonium sulphate instead of a saturated solution of ammonium chloride. Folin's method is expeditious, but I do not think it is reliable when the urine is concentrated, and it was found with the dilute urine of my patient that two hours were insufficient for complete precipitation. The uric acid was observed to be increased while the patient was taking salicylate of soda, and, to a slight extent, during the administration of euonymin. Noel Paton found that euonymin increased while salicylate and benzoate of soda markedly diminished the excretion of uric acid. Hopkins, in Schäfer's *Physiology*, states that the salicylates undoubtedly increase the quantity of uric acid in the urine.

For estimating creatine Johnson's method was adopted, but a very small amount of the mercurial compound always adhered to the flask, hence a margin of error is introduced into the result.

For the estimation of ammonia Schloesing's method was adopted, but it is unsatisfactory for clinical purposes because of the length of time required. As the urea kept persistently below the normal in this case, it was considered probable that the ammonia would be increased in consequence of the diminished formation of urea. Neubauer found the quantity of ammonia to vary in health from 0.3 to 1.2 g. in the twenty-four hours, and this has been confirmed by later observers. In my patient it varied from 1.04 to 1.4 g., but it is doubtful whether this slight augmentation is due to the feeble reaction of the urine or to diminished functional activity of the liver.

SUMMARY OF CONCLUSIONS.

1. The amount of bile secreted in the twenty-four hours in a man somewhat below medium height and weight averages 775 c.cm. and the bile solids 15.8 g.
2. More bile is secreted during the day than at night.
3. The sulphocyanate of potash in the saliva is not derived from the biliary salts.
4. The following substances increase both the quantity of bile and bile solids—Old Sulphur Spring (Harrogate) Carlsbad mineral water, euonymin, benzoate of soda, salicylate of soda, and Kissingen Spa (Harrogate).
5. Podophylloresin and iridin augment the bile solids without appreciably affecting the quantity of bile.
6. Strong Montpellier Spring (Harrogate) and podophyllo-toxin appear to diminish slightly both the quantity and the solids.
7. Hot water and soda water in pint doses do not seem to increase the biliary secretion.
8. Salicylate of soda increases the excretion of uric acid in the urine.

REFERENCES.

- 1 Monro, *Cyclopædia of Anatomy and Physiology*, London, 1839-1847, p. 180.
- 2 Charles Robin, *Leçons sur les Humeurs Normales et Morbides du Corps de l'Homme*, Paris, 1867.
- 3 Harley, *Med. Chirurg. Trans.*, 1866, p. 89.
- 4 Murchison, *Diseases of the Liver*, third edition, p. 576.
- 5 Frerichs, *Klinik der Leberkrankh.*, Bd. II, p. 130.
- 6 Ranke, *Die Blutvertheilung und die Thätigkeitwechsel der Organe*, Leipzig, 1871, chap. viii.
- 7 Noel, *Journal de Pharmacie et de Chimie*, III, vol. xxxi, p. 354, Paris.
- 8 Von Wittich, *Arch. d. ges. Physiol.*, Bd. vi, p. 181.
- 9 Westphalen, *Deut. Arch. f. klin. Med.*, vol. xi, p. 588.
- 10 Yeo and Herroun, *Journal of Physiology*, vol. v, p. 116, 1884.
- 11 Hammersten, *Maly's Jahres-Bericht der Thier-Chemie*, 1894, p. 331.
- 12 Edington, *Journal of Anatomy and Physiology*, 1896.
- 13 Copeman and Winston, *Journal of Physiology*, vol. x, p. 213.
- 14 Mayo Robson, *Proceedings of the Royal Society*, vol. xlvii, p. 499.
- 15 Noel Paton and Balfour, *Laboratory Reports, Royal College of Physicians, Edin.*, vol. iii, 1891.
- 16 Paton, *Laboratory Reports, Royal College of Physicians, Edin.*, vol. iv, 1892.
- 17 Pfaff and Balch, *Journal of Experimental Medicine*, New York, January, 1897, p. 49.
- 18 Gamgee, *Physiological Chemistry of the Animal Body*, vol. ii, p. 277.
- 19 Fenwick, *The Saliva as a Test for Functional Disorders of the Liver*, 8vo, London, 1889.
- 20 J. H. Nasse, *Commentatio de Biliis Quotidie a Cane Secreta Copia et Indole*, quoted by Rutherford.
- 21 Kolliker and Muller, *Beitrag zur Lehre von der Galle*, Würzburg *Verhandlungen*, vol. v, 1855.
- 22 Mosler, *Virchow's Archiv*, Bd. xlii, p. 29, 1858-59.
- 23 G. Scott, *Beale's Archives of Medicine*, vol. i, p. 209.
- 24 Hughes Bennett, *British Association Reports*, 1868.
- 25 Röhrig, *Experimentelle Untersuchungen über die Physiologie der Gallenabsonderung*, *Wiener Med. Jahrbücher*, 1873, p. 240.
- 26 Rutherford, *Transactions of the Royal Society, Edinburgh*, vol. xxix, 1870.
- 27 Rosenberg, *Pfuger's Archiv*, 1890, Bd. xli, p. 334.
- 28 Battistini, *Moleschott's Untersuchungen*, xlii, p. 414, 1888.
- 29 Marfori, *Su la Pretesa Azione Colagoga della Santonin*, *Annali di Chimica e di Farmacologia*, Ser. 4, vol. x, p. 153.
- 30 Prevost and Binet, *Recherches Experimentales relative à l'Action des Médicaments sur la Sécrétion Billaire*,

et à leur Elimination par cette Sécrétion, *Revue Médicale de la Suisse Romande*, No. 520, Mai, 1888.

³¹ Baldi, *Archives Ital. de Biologie*, t. iii, p. 389.

³² Kunkel, *Pfuger's Archiv*, xv, p. 353.

³³ Lewaschew, *Ztschr. f. klin. Med.*, Berlin, 1884, Bd. viii, S. 67.

³⁴ Paschki's Ueber Chologoga, *Med. Jahrbücher*, 1884, p. 159.

³⁵ Niessen, *Maly's Jahresbericht*, 1890, p. 280.

³⁶ Mandelstamm, Ueber den Einfluss einiger Arzneimittel auf Secretion und Zusammensetzung der Galle, *Inaug. Diss. Dorpat*, 1890.

³⁷ Müller, Ueber den Einfluss einiger pharmakologischer Mittel auf Secretion und Zusammensetzung der Galle, *Inaug. Diss. Dorpat*, 1890.

³⁸ Loewenton, Experimentelle Untersuchungen über den Einfluss einiger Abführmittel und der Clysmata auf Secretion und Zusammensetzung der Galle, sowie deren Wirkung bei Gallenabwesenheit in Darne, *Inaug. Diss. Dorpat*, 1891.

³⁹ Glass, Ueber den Einfluss einiger Natron-Salze auf Secretion und Alkaliengehalt der Galle, *Inaug. Diss. Dorpat*, 1892, and *Archiv f. exp. Path. u. Pharmak.*, vol. xxx (1892), pp. 241-247.

⁴⁰ Stadelmann, *Therapeutische Monatshefte*, 1891, p. 511.

⁴¹ Gamgee, *Textbook of Physiological Chemistry*, vol. ii, p. 374.

⁴² Dunstan and Henry, *Chemical Society's Transactions*, March, 1898.

⁴³ Paton, *BRITISH MEDICAL JOURNAL*, 1886, vol. i, p. 435.

⁴⁴ Neubauer, *Journal f. prakt. Chem.*, Leipzig, 1852, Bd. lxiv, S. 177.

THE EFFECT OF EXERCISE ON THE HÆMOGLOBIN WITH REFERENCE TO THE VALUE OF REST IN THE TREATMENT OF ANÆMIA.

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The observations made by G. Oliver and the writer, and published by the former in the Croonian Lectures for 1896,¹ have shown the occurrence of a diurnal physiological variation in the blood of healthy subjects, a fall in the percentage of hæmoglobin, corpuscles, and of the "worth" of the corpuscle taking place during the day, and a rise during the night.

Chart 1, taken from a continuous chart of observations on another subject is a typical example of the normal daily variations.

Examination of 650 observations on two subjects gave an average daily variation in hæmoglobin of 7.3 per cent. (7.4 per cent. day fall and 7.2 per cent. night rise); in the volume of the corpuscles of 4.3 per cent.; and, consequently, a variation in the "worth" of the corpuscle which averaged 5.9 per cent. (5.7 per cent. day fall and 6.1 per cent. night rise). The fall in "worth" is an indication of actual loss of hæmoglobin, in addition to the apparent loss resulting from dilution of the blood by fluids ingested during the day; a loss which is probably brought about by the wear and tear of the process of oxidation. It is interesting to note that the average night rise (6.1 per cent.) in the worth of the corpuscle is slightly in excess of the average day fall (5.7 per cent.), providing probably a slight reserve of hæmoglobin in the animal economy to meet variable calls made upon it, such as exercise, as will be seen below.

The amount of variation of the hæmoglobin almost always exceeds that of the corpuscles; hence a variation takes place in the "worth," the latter being a theoretical value obtained by dividing the percentage of hæmoglobin by the percentage volume of corpuscles.

It then became a matter of interest to determine whether the process was reversed in a subject who worked during the night and rested during the day. This was found to be the case.

Chart II shows the result of observations made on the blood of a hospital nurse aged 22 for a fortnight, the first half of which she was on day duty, the second half on night duty. (The readings were taken immediately after rising and before retiring to rest.)

When on day duty the blood showed the usual variation of day fall and night rise; when on night duty a day rise and night fall. It is interesting to note that the average fall in the worth of the corpuscle while on day duty (4.8 per cent.) is greater than that which occurred while on night duty (3.2 per cent.), the difference being probably accounted for by the fact that the amount of muscular work performed was distinctly less in the latter case than in the former. The effect of exercise given below tends to confirm this view.

ACTIVE EXERCISE.

The effect of exercise appears to be to cause a distinct fall in the "worth" of the corpuscle, or a loss of hæmoglobin.

To determine further the effect of exercise an examination of a continuous record of daily morning and evening observation of the blood of a healthy subject, extending over a period of three and a-half months, gave the following results. The average daily fall in the worth of the corpuscle on sixty-five days on which no exercise was taken amounted to 6.1 per cent., while the average fall on thirty-five days on which exercise was taken amounted to 9.1 per cent., showing an increased fall of 3 per cent. on exercise days over no exercise days. The exercise taken varied in kind and amount, but on each of the thirty-five days it was considerable. The primary effect, then, of exercise appears to be to increase the normal day fall.

Chart III shows two examples of the result of exercise, the first (2 hrs. cycling and horse riding) without sensible perspiration, the second (2 hrs. hard tennis) with profuse perspiration.

In each case a fall in percentage of hæmoglobin took place, with a rise in percentage volume of corpuscles, and, consequently, a fall in the "worth" of the corpuscle. Where profuse perspiration occurred the rise in percentage of corpuscles is considerable, due partly to concentration of the blood by withdrawal of fluid; hence the fall in worth in this case, the exercise being more violent, is greater than in that where no sensible perspiration took place.

Similarly the average night rise in the worth of the corpuscle that succeeded the day fall on exercise days amounted to 9.3 per cent.; whereas the night rise succeeding the day fall of no-exercise days only amounted to 6.1 per cent., a gain of 3.2 per cent. rise after exercise. Thus the augmented day fall is followed by an augmented night rise. Comparing these two we find that the average increase in the night rise after exercise (3.2 per cent.) is in excess of the average increased fall that immediately follows exercise (3.0 per cent.), which tends to show that the latter has a secondary effect in stimulating the formation of hæmoglobin.

This position is corroborated by a further examination of the record. The morning observations (when the blood is at its highest point) of the days immediately following exercise were compared with the morning observations of the exercise days themselves; and similarly the morning readings of the days following no exercise were compared with those of the previous mornings, with the object of determining whether the worth of the corpuscle was higher on the morning after exercise than on the morning of the day of exercise itself; or lower on a morning after a no-exercise day than on the morning of the no-exercise day itself, with the following results:

Morning Readings following Exercise Days compared with Morning Readings of Exercise Days themselves. Thirty-five Observations.

- Worth of corpuscle higher on the following morning than on previous: 10 times, or 28.5 per cent. average increase, 2.8 per cent.
- Worth of corpuscle lower on the following morning than on previous: 15 times, or 42.9 per cent. average decrease, 1.8 per cent.
- Worth of corpuscle equal on both occasions: 10 times, or 28.5 per cent.

Morning Readings following no-Exercise Days compared with Morning Reading of no-Exercise Days themselves. Sixty-five Observations.

- Worth of corpuscle lower on following morning: 21 times, or 32.3 per cent. average decrease, 2.5 per cent.
- Worth of corpuscle higher on following morning: 25 times, or 38.4 per cent. average increase, 2.1 per cent.
- Worth of corpuscle equal on both occasions: 19 times, or 28.7 per cent.

Average increase of 0.7 per cent. following exercise.
" decrease of 0.7 per cent. " no exercise.

This was in one way contrary to expectation, for the worth of the corpuscle read higher on the morning after exercise days than on the morning of the exercise days only ten times, whereas it read lower 15 times, being equal ten times in 35 observations. Also the worth of the corpuscle on the morning following no-exercise days read lower than on the previous morning less frequently (21 times) than it read higher (25 times), thus tending to show a greater formation of hæmoglobin as the result of no exercise than of exercise. But comparing the average amount of increase and decrease in the two cases, the reverse is seen to be the case. For the average increase after exercise days (when an increase took place) amounted to 2.8 per cent., while the average increase after no-exercise days amounted to only 2.1

per cent., a gain of 0.7 per cent. in favour of exercise. And further, the average decrease after exercise days (when a decrease took place) only amounted to 1.8 per cent., while the decrease after no-exercise days amounted to 2.5 per cent., a gain once more (in the shape of a lesser fall) in favour of exercise of 0.7 per cent.

These figures being so small, the actual amount of gain may appear trivial, but it must be borne in mind that the cumulative effect of even so small an increment must have a powerful influence in maintaining a high average level of the worth of the corpuscle.

Thus exercise appears to result in a temporary increased destruction of hæmoglobin, but to be followed by a more than corresponding increased formation; in the healthy subject its remote effect is to stimulate the production of hæmoglobin. Possibly this may be the cause of the reserve of hæmoglobin mentioned above as being stored up to provide against contingencies. That exercise causes a not inconsiderable temporary drain on the resources of the hæmoglobin the above figures abundantly demonstrate, and the advantage of a slight reserve becomes apparent.

If these conclusions be correct, it follows that during a period when little or no exercise is taken, the average level of the worth of the corpuscle must be below that of a period of the same length during which frequent exercise is taken. The record was examined on this point with the result that during the month of August, when the subject was taking frequent hard exercise, the average of the morning readings of the worth gave the figure 1.076; during September, when a moderate amount of exercise was taken, 1.052; while during October, when circumstances compelled the subject to lead an almost absolutely sedentary life, the average amounted to 1.03.

PASSIVE EXERCISE.

That passive exercise in the form of massage causes a rise in the percentage of corpuscles has been noted by several observers, among them being Melassez,² Chéron,³ and K. Mitchell.⁴ The latter noticed an increase in the number of corpuscles, sometimes very considerable, after massage, the maximum being reached one hour after cessation of the process, but he failed to find a corresponding increase in hæmoglobin. The rise in corpuscles he attributes to the dislodgement of large numbers that are sluggishly lingering in the by-ways of the circulation, and not available for use until disturbed by the massage.

Chart IV.—Massage: A. Heavy movements (40 mins. to limbs and body). B. Light movements (40 mins. to limbs and body).

Chart IV shows in graphic form the result of two typical experiments. They agree with the observations made by Mitchell as regards the corpuscles, the volume of which is increased, the maximum being reached one hour after light massage and two hours after heavy massage. But a corresponding rise in the percentage of hæmoglobin was noted, with, consequently, no change in the worth of the corpuscle. This result is probably due to a diminution of the total volume of the blood, fluid passing out through the capillary wall to supply the place of lymph driven on by the massage, and not to the passage of stagnant corpuscles into the active circulation. The diminution was greater after heavy than after light massage, and persisted for some hours before the displaced fluid found its way back into the general circulation, and restored the blood to its original volume. In no case was a fall in the worth of the corpuscle observed after massage. Moreover, a prolonged course of massage

(one hour twice a day) on a subject whose blood decimal, or worth, was normal, had no effect in either raising or lowering it. Before the course the blood averaged $\frac{88 \text{ hæmoglobin}}{88 \text{ corpuscles}} = 1.00$ worth; after three weeks' massage

it rose to $\frac{109}{109}$, and after six weeks' massage it fell to $\frac{98}{98}$, about which point

it remained. The volume of the blood was thus considerably diminished, and massage, therefore, is a powerful agent in promoting the transudation of fluid through the capillary walls, but apparently has no effect in causing destruction of the hæmoglobin.

In this connection it may be noted that Lloyd Jones⁵ inclines to the belief that many cases of chlorosis are characterised by an increase in the total volume of the blood, and he quotes Rubenstein⁶ as holding the same opinion. The effect of massage in reducing this may account to some extent for the benefit derived by many of these patients from its use.

EFFECT OF REST.

The next point determined was the effect of rest on the blood. With this object the blood of a normal subject (female) was examined night and morning for a considerable period, during which she was performing her ordinary avocation, which entailed a fair amount of exercise, walking and cycling. She was then put to bed, and remained there for five days, after which she resumed her usual course.]

Chart V summarises the results obtained. It is a portion of the complete chart of the subject in question, and embraces ten days previous to rest, five days in bed, and ten days subsequently.

The general average of the readings is seen to be somewhat below the normal of 100. This is usually the case in female subjects. During the first period of ten days the hæmoglobin and corpuscles showed the customary variations of day fall and night rise, the variation in hæmoglobin being relatively greater than that of the corpuscle, hence the variation in the worth of the corpuscle; the average day fall for the ten days being 4.45 per cent. During the period of five days' rest similar variations in hæmoglobin and corpuscles took place, but they are more nearly related to one another, hence the variation in the worth becomes less than before, the average fall for the five days being only 1.2 per cent. The factor of exercise being eliminated, the destruction of hæmoglobin that occurs in the day becomes much less than when the subject

is leading her ordinary life. The period of ten days subsequent to rest show a return to the normal condition, the average fall in worth being 5.35 per cent., rather greater than before. The general average of the readings of hæmoglobin and corpuscles fell somewhat during the period after rest, but as the worth remains at about its mean of 1.00 the fall merely implies a temporary increase in the volume of the blood.

A further point of interest lies in the gradual steady increase in the worth that occurred during rest. Regarding the morning observations alone as being the readings taken when the blood is presumably at its steady point, a gradual rise takes place from 0.99 to 1.02, when it attained its maximum and remained there for three days, falling after activity was resumed to its mean of 1.00. Whether this high level would have been maintained through a prolonged period of rest is doubtful.

To summarise briefly the above facts:

1. There is a normal day fall and night rise in the worth of the corpuscle, representing a daily destruction and regeneration of hæmoglobin.

2. Active exercise increases the extent of the day fall and night rise.

3. Active exercise stimulates a slight over-production of hæmoglobin.

4. Passive exercise (massage) diminishes the volume of the blood, but has no effect in diminishing or increasing the amount of hæmoglobin.

5. Rest reduces the extent of the day fall in worth, representing a diminished destruction of hæmoglobin.

The bearing of these facts on the treatment of anæmia is obvious, providing as they do a physiological foundation for the well-known value of rest in bed in the treatment of that affection. Inasmuch, however, as the effect of exercise is to stimulate the production of hæmoglobin, while that of rest is to lessen its destruction, it may be objected that the conclusions to be drawn from these data are in mutual contradiction. It must be borne in mind, though, that the observations were made on normal subjects, in whom the temporary increased destruction of hæmoglobin brought about by exercise is fully met and repaired by increased formation. To complete the investigation it is necessary to determine by diurnal observation of the blood of an anæmic subject taking considerable exercise, whether the reproduction of the hæmoglobin would be sufficient to make good the loss occasioned by exercise. The undesirability of keeping a patient sufficiently long under observation without treatment has prevented me examining this point. From clinical experience we may infer with tolerable certainty that construction would fall short of destruction, or at least would not be in excess of it as is the case in health. In other words, that the already seriously diminished amount of hæmoglobin would be unable to respond to the call made upon it by exercise, so that gradually the total amount would be further lessened. Rest, on the other hand, by removing the drain, would enable the constructive process to exceed the destructive, and the store of hæmoglobin to be gradually built up.

MODE OF OBSERVATION.

The instruments used in the collection of these data were the hæmoglobinometer and hæmocytometer devised by Oliver.¹

REFERENCES.

- ¹ Croonian Lectures, *Lancet*, vol. i, 1896. ² *Compt. Rend. Soc. Biol. Paris*, tomes cxl, cxlii. ³ *Compt. Rend. de l'Acad. des Sciences*, 1895, vol. ii, No. 6. ⁴ Allbutt's *System of Med.*, vol. i, p. 378. ⁵ "Chlorosis," by E. Lloyd Jones, p. 24. ⁶ "Ueber die Ursache der Hellwirkung des Aderlasses, bei Chlorose," *Wien. Med. Presse*, 1893.

THE ROYAL BERKSHIRE HOSPITAL.—The Prince of Wales, on the occasion of his visit to Reading on June 11th to open Reading College, visited the Royal Berkshire Hospital. The Prince, who was accompanied by Prince Christian and Lord Wantage, Lord Lieutenant of Berkshire, was received by the Vice-President, by the Senior Physician, Dr. Marriott, and by the Senior Surgeon, Mr. Maurice, by whom he was conducted through the various wards, the other members of the medical staff being present. The Prince spoke sympathetically to several patients, and remarked on the cleanliness, cheerfulness, and capacity of the wards, and commended the open air verandahs at the end of each ward which are used for convalescent patients.

A CASE OF EXOPHTHALMIC GOITRE WITH UNILATERAL EYE SYMPTOMS.

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EXOPHTHALMIC GOITRE is a disease which of late years has been the subject of much difference of opinion as to etiology, pathology, and treatment. Many of the disputed points can only be solved by the lessons of clinical experience, and hence the value of the clinical record of any case of exceptional character. The following case, presenting several features of great clinical interest and rarity, has seemed to me worthy of special record and comment.

J. W., an unmarried woman, aged 24 years, came to the Glasgow Eye Infirmary on February 11th, 1898. She stated that since the beginning of this year her friends had been calling attention to the peculiar prominence and staring appearance of the left eye, which had gradually become more and more pronounced. About the same time her attention was also called to the fact that there was a distinct swelling of the throat, which had gradually become worse. Since the appearance of these symptoms she had felt somewhat nervous, being more easily excited and startled than she used to be. But in other respects she had felt quite well.

Her left eye had a prominent and staring appearance, which gave the patient a very peculiar look. There was slight exophthalmos, but what gave the eye its peculiar appearance was a strong retraction of the upper lid (Stellwag's symptom), so that the palpebral aperture was very much greater than on the other side. On asking the patient to look downwards, there was but little descent of the upper lid, while the globe rotated downwards in a normal manner (Graefe's symptom). The appearance and movements of the right eye were normal. A considerable uniform enlargement of the thyroid gland was found. There was no tachycardia, the pulse being about 72 per minute, and no history of palpitation. The patient was well coloured, and there was no menstrual disturbance.

She was put upon gradually increasing doses of antipyrin, beginning with 5 grains thrice daily, and decided improvement was evident within three weeks of the commencement of the treatment. She was shown at a meeting of the Glasgow Medico-Chirurgical Society on March 18th, 1898, and the following is a brief statement of her condition: The exophthalmos and retraction of the upper lid of the left eye have disappeared, so that when the patient looks straight forward there is no difference observable between the two eyes. In fact she is cured of the disfiguring appearance for which she sought relief. When she looks downwards, however, there is still very defective descent of the left upper lid—that is, the Graefe's symptom has persisted unchanged. The enlargement of the thyroid is very markedly diminished, although yet quite distinct. She feels better as regards the nervousness since the antipyrin treatment was begun.

Although there was here no increased frequency of the heart's action, the symptom, which is generally regarded as the most constant, and that which occurs earliest, still there can be little doubt that here we have a case of exophthalmic goitre in the early stage. The three classical symptoms, the tachycardia, the enlargement of the thyroid, and the exophthalmos do not appear simultaneously, and the degree of completeness of the clinical picture will depend upon the stage of the disease at which the patient is first seen. When the disease is fully developed the diagnosis is easy, but in the early stages, the true character of such atypical cases is apt to be overlooked, and yet here the diagnosis is of the utmost importance, since it is at this stage our opportunities of successful treatment are greatest. Hence the importance of knowing that unilateral exophthalmos may be the first symptom of this disease. Two years ago I saw in private a case precisely similar to the present, where unilateral exophthalmos was the first and most striking symptom of the disease. The patient was a young lady, and consulted me with reference to the disfiguring appearance of a staring and prominent left eye. Here, too, the presence of Stellwag's and Graefe's symptoms made the diagnosis clear, which was further confirmed by a slight fullness of the thyroid and slight tachycardia. Hence in every case of unilateral exophthalmos the possibility of its being a manifestation of exophthalmic goitre should always be borne in mind, and the patient carefully examined.

A point of great interest in this case is the disappearance of the retraction of the upper lid (Stellwag's symptom), whilst the non-simultaneous descent of lid and globe of eye remains unchanged (Graefe's symptom). These two symptoms are commonly regarded as being due to the same cause, namely, spasm of Müller's muscle, those unstriated muscular fibres in the upper lid which are supplied by the sympathetic. The complete disappearance of the one symptom while the other remains unchanged clearly