7. The comparatively slow reduction in the size of the spleen, while it is not being directly treated, may be a factor in keeping the leucocyte count high. This is in a measure advantageous, as it guards against stopping the treatment too soon. The count will not become normal while the spleen is still enlarged and is still diminishing in size.

8. That actual destruction of the splenic tissue results from the cumulative effect of direct x-ray exposures is, in a measure, disproved by the following observations:

(a) The spleen is diminished in size by applications to the bones alone.

(b) In all of our cases which have reacted favorably to the treatment, it has been noted that after the spleen has been included in the applications, the first or second exposure in each series is usually followed by a decided rise in the count, associated very often with evidences of more or less diminution in the size of the tumor. A third or fourth exposure usually brings the count down again by a destruction of the lymphocytes in the circulation. These facts would seem to indicate some direct connection between the decrease in the size of the spleen and the increase in leucocytosis and lymphocyte percentage.

(c) In the first patient seventeen, almost daily, splenic applications of short duration, made before starting the bone-marrow treatment, reduced the leucocyte count from 386,000 to 133,000, with a relative increase in myelocytes from 16 $\frac{2}{3}$ per cent. to 25 $\frac{1}{2}$ per cent., but there was comparatively little diminution in the size of the spleen.

(d) In the two unfavorable cases with acute relapses, repeated direct applications had no effect whatever on the spleen, which continued to grow larger. At the same time the leucocyte count rose rapidly, although the first one or two direct splenic exposures were followed by a decided drop, which lasted for a day or two only. It may be well to explain that the reason for these direct splenic exposures was the fact that bone-marrow applications had no effect whatever in checking the extremely rapid enlargements of these spleens, and it was hoped that comparatively short and safe direct exposures might have some such influence. So rapid was the enlargement in one of these two cases that death occurred very suddenly, following phenomena which may have been due to a rupture of the spleen.

9. A peculiarity of this treatment is the fact that the patient may feel perfectly well, but still have a moderately high leucocytosis and a comparatively large spleen. In our first case, after 112 treatments during a period of ten months, the count still averages from 75,000 to 100,000, with 3 to 4 per cent. of myelocytes, and the spleen is still moderately large, but the patient feels as well as he ever did in his life, and is able to attend to all of his work. He has been in this condition for the past four months. His leucocytosis decreases very slowly, but a slight drop is noted each time a new area is exposed in its turn, as compared to the count at the time of the previous series to the same part. The only explanation for this long continued high leucocytosis is that in its slow but steady decrease in size the spleen, which receives but comparatively few direct exposures, pours out large numbers of lymphocytes into the circulation, where they are destroyed slowly. The presence of 3 to 4 per cent. of myelocytes shows that this patient is still far from well.

10. Daily exposures, when not contraindicated, may frequently yield quicker and better results. The slow

progress made by the case just mentioned may be accounted for by the fact that he received but three treatments per week, and for a while only two. Our most favorable case was treated daily.

11. All cases will not respond to even this method of treatment. In acute primary attacks and relapses x-ray treatment is perhaps, as a rule, contraindicated.

12. Lymphatic cases also respond well to this method of treatment. It is advisable to observe the same precautions in regard to applications to the glands as those mentioned in connection with the spleen.

13. Cessation of treatment for long intervals is to be guarded against, especially in the early stages. Even short interruptions are not advisable until the disease is well under control.

14. The proper time to stop treatment is still a somewhat uncertain question. The frequency of the applications should not be lessened until the general condition is normal and the size of the spleen and the leucocyte count nearly so. It would seem wiser to stop gradually rather than abruptly.

15. The leucocyte count, *per se*, becomes a matter of minor importance, but the differential count is always one of the important indices to the effect of the treatment. The failure of the count to drop, after the third application in the series to any particular area, to a point as low as or lower than before the first, has been taken of late as an indication to give more than the three customary exposures to that part. As conditions begin to indicate the approach of a cure this tendency of the leucocytosis to increase becomes less marked.

16. The distribution of the applications over almost the entire body renders the risk of a severe dermatitis, with ordinary care, very slight.

17. The bone pains, noted especially in splenomedullary cases, are relieved early by this method of treatment.

COMPARATIVE POTENCY OF HYOSCIN AND SCOPOLAMIN HYDROBROMID IN REFRACTION WORK.*

WENDELL REBER, M.D.

PHILADELPHIA.

Some years ago in some notes¹ on the mydriatic alkaloids I made mention of a youth of 16 with emmetropic eyes on whom I had tested the effects of hyoscin hydrobromid and scopolamin hydrobromid. One drop of a 1/10 per cent. solution of the hyoscin salt was used in the right eye and one drop of a 1/10 per cent. solution of the scopolamin salt was used in the left eye. The effect of the two drugs on the pupil is shown in Figure 1 and on the ciliary muscle in Figure 2. From these results I leaned to the conclusion that the two drugs were practically identical in action and, therefore, interchangeable, and I so put myself on record at that time. For some time afterward I ordered 1/10 per cent. of solutions of scopolamin or hyoscin hydrobromid indiscriminately in my office refraction work, but it was not long before the scopolamin cases began to show uncertain cycloplegia, while the hyoscin cases seemed to be much surer in result. Cases were, therefore, sought out that offered favorable conditions for further pharmacodynamic comparative tests of the two drugs. Within

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1. American Jour. Phar., 1899.

two years three persons were found who were so doubtful about the acceptance of even a plus 0.25 D. sphere (under cycloplegia) as to fit them for these tests. One showed two degrees of esophoria, one showed one degree of esophoria and one lateral balance. The first was 26 years of age, the second 22 years of age and the third 20 years of age. In the right eye of each of these patients was instilled one drop of a 1/10 per cent. solution of hyoscin hydrobromid (Merck) and in the left eye of each patient one drop of a 1/10 per cent. solution of scopolamin hydrobromid (Merck). These solutions were prepared for me by Messrs. Shinn & Kirk, of

all other minutiae so arranged as to eliminate the possible sources of error. The effect on the pupil in each case is shown in Figures 3, 4 and 5, while the effect on the range of accommodation in each eye is shown in Figures 6, 7 and 8.

PUPILS.

By reference to the figures it will be seen that the average time of beginning action on the pupil was ten minutes for both of the drugs in all of the eyes. Full dilation of the pupil occurred in the 22- and 26-year-old females in 30 minutes with hyoscin and in the 20-year-old male in 45 minutes. This may be attributed to the fact that the sympathetic nervous system is much more active in females than in males. The same difference in pupillary response was observable with the scopolamin. In the two females full pupillary dilation under scopolamin occurred in 40 minutes and in the male in 60 minutes.

Fig. 1.—Effect on accommodation; T. K., aged 16. Scopolamin solid; hyoscin dotted.

Fig. 2.—Effect on pupil. Scopolamin solid; hyoscin dotted.

Fig. 3.—Effect on pupil.

Fig. 4.—Effect on pupil.

Philadelphia, who dissolved the drug in saturated boric acid solution and then filtered the solution. Mr. Kirk himself exercised particular care in their preparation, as he had been told that they were to be used for experimental purposes. The two solutions were stood for three minutes in a flat-bottomed shallow bowl of water brought to a temperature of 80 F. A standard dropper was used, and after use in the right eye was carefully washed out before using for the left eye. Hyoscin was used in each case in the right eye and scopolamin in the left eye and

The pupils of the 20-year-old male were 0.5 mm. smaller in both eyes at the start.

According to these findings, therefore, hyoscin showed an average time of 35 minutes to produce full pupillary dilation in the three cases, while scopolamin showed an average time of 47 minutes to produce the same result.

ACCOMMODATION.

In Figures 6, 7 and 8 is plotted by curves the effect on the accommodation of each eye of the three cases tested.

The curve indicating the hyoscin effect is shown by the broken line, while a solid line shows the scopolamin effect on the same patient.

In Figure 6 it will be noted that full cycloplegia was established in the right eye by one drop of the 1/10 per cent. hyoscin solution in 50 minutes, while an equal amount of scopolamin salt in the other eye did not bring about full cycloplegia until the expiration of 70 minutes.

In Figure 2 the onset of full cycloplegia also occurred in 60 minutes, while scopolamin in equal dose required 120 minutes to produce the same effect. In Figure 8 hyoscin produced full cycloplegia in 50 minutes and

59:92. Or, to reduce it to the commoner form of statement, hyoscin in these test cases showed itself approximately 50 per cent. more potent than scopolamin in producing cycloplegia for refraction work. So much for the academic phase of the matter which seems to be rather at variance with the claims which chemistry makes for these two drugs.

CHEMICAL CONSIDERATIONS.

Since 1833, when Phillip Geiger announced that, along with Hesse, he had succeeded in obtaining from some domestic poisonous plants the alkaloids atropin, hyoseyamin and daturin, down to the present day there have been not only numerous additions to this alkaloidal family, but there has continued a more or less animated

Fig. 5.—Effect on pupil.

Fig. 7.—Effect on accommodation; Miss C., aged 22.

Fig. 6.—Effect on accommodation; Miss M., aged 26.

Fig. 8.—Effect on accommodation; W. J., aged 20.

scopolamin in 100 minutes. If to these 3 cases we add the results in Case 1 above alluded to (Fig. 2) we find that:

The average time for onset of full cycloplegia under hyoscin (1/10 per cent. solution) in 4 cases was 59 minutes.

The average time for onset of full cycloplegia under scopolamin (1/10 per cent. solution) in 4 cases was 92 minutes.

So that the relative pharmacodynamic power of hyoscin hydrobromid and scopolamin hydrobromid as used in ordinary office work may be said to be somewhere close to

discussion as to the properties of the several principles and the identity or non-identity of a number of them. Among the many alkaloids, acids and bases that have been derived from the Solanaceæ may be mentioned atropin, tropin, atropic acid, tropic acid, hyoscin, hyoscin acid, duboisin, homatropin, oxytropin, scopolamin, daturin, scopolin, oscin and atosin.

One stands bewildered at the multiplicity and seeming interchangeability of the various bases and salts, and this confusion was not a little confounded when hyoscin hydrobromid was made official in the third edition of the

German Pharmacopeia and the same chemical was designated as scopolamin (by the influence of E. Schmidt) in the 1895 supplement to the same.

Pinner² makes the following statements concerning the chemistry of this alkaloid family:

1. The different members of the Solonaceæ, namely, atropa, hyoscyamus, datura, mandragora, solanum and anisodus, contain two principal alkaloids, one of the composition of $C_{17}H_{23}NO_3$, the other of the composition $C_{17}H_{21}NO_4$, so that the second may be viewed as an oxidation product of the first.
2. The first mentioned is hyoscyamin, which is easily convertible by alkalis into atropin. While the latter principle may exist as such in small quantities in the above-mentioned species, it is altogether possible that hyoscyamin is the form the alkaloid takes in the living plant, while atropin is the form in which it appears in the dead plant.
3. The second base is hyoscin, or what amounts to the same thing—scopolamin. It would appear that in the presence of alkalis, hyoscin undergoes a change similar to that of hyoscyamin, and then becomes inactive atrosicin.
4. Further, hyoscyamin and atropin by separation of a molecule of water, become apo-atropin or atropamin, which is isomeric with belladonnin.
5. Hyoscin is derived principally from the root of scopolia atropoides, and contains in addition to hyoscin, inactive atrosicin and traces of hyoscyamin and atropin.
6. Finally, there is present in duboisin, not only hyoscyamin, but also hyoscin and other alkaloids.

The 1900 edition of the U. S. Pharmacopeia affords no help in the attempt to clear up the question. For both hyoscin and scopolamin hydrobromid it gives the formula $HBrC_{17}H_{21}NO_4 + 3(H_2O) = 434.92$.

Fifteen works on materia medica and therapeutics were gone through and every one of them stated in substance that hyoscin and scopolamin hydrobromid were identical of composition and effect.

As Merck's chemicals had been used in the experiments, the firm of Merck & Co. in New York City were then appealed to and they wrote as follows:

Referring to your favor of the 9th instant, we would say that the formulas for hyoscin hydrobromid and scopolamin hydrobromid are alike as stated in the U. S. Pharmacopeia for 1900. This view of chemical identity seems to be pretty generally accepted now, although ten years ago the question was very unsettled. It occurs to us that the difference in the strength of hyoscin hydrobromid and scopolamin hydrobromid, which you noticed in your experiments, may be due in part to the fact that some makes of scopolamin hydrobromid on the market are of comparatively low specific rotatory power, and it has been held that the higher the specific rotatory power, the greater the physiologic effect of the product. For instance, the specific rotatory power of scopolamin hydrobromid (Merck) is about -20 degrees, whereas that of another make tested only about -6 degrees, and our works report that some brands test as low even as -2 degrees.

As this did not entirely satisfy the conditions under which the experiments were made, Merck & Co. were again written to the effect that the hyoscin and scopolamin salts used in the test were both of their own manufacture and the specific rotatory power of hyoscin hydrobromid was asked for. Merck & Co. again replied, stating this time that scopolamin hydrobromid (Merck) and hyoscin hydrobromid (Merck) were both of a specific rotatory power of -20 degrees.

This leaves the matter precisely where it was in the beginning, namely: that with two drugs said to be absolutely identical as to clinical effect, pharmacodynamic power, molecular build and reaction with the polariscope, there should seem to be a more or less uniform difference

in potency when tested by the delicate accommodation reaction.³

There remains as a possible explanation the parallel fact of chemical identity but pharmacodynamic difference in the effect of caffeine and thein [both of the formula $C_8H_{10}N_4O_2(C_2H_4O_2)_2$], also of cocaine and stovaine, which are said to be chemical isomers and yet exhibit wide difference in their action. The familiar example of the kaleidoscope naturally occurs to one pondering such problems. Although the number of pieces of glass in the instrument never changes, yet how varied the changes in the effect to be had by rotating the instrument. It requires but a slight stretch of the imagination to believe that some such similar principle may be operative among chemical isomers. That is to say that, although they may be of the same total molecular constitution, yet a different arrangement of the various molecules may result in difference of therapeutic effect or biologic reaction, just as one dozen dry or wet batteries produce currents of varying qualities according to the way in which they are connected, a fact utilized by electricians every day.

Unless some such possible explanation as that just offered exists there is no means of explaining the seeming difference in the reaction of the eye to hyoscin and scopolamin hydrobromid.

CLINICAL CONSIDERATIONS.

In the last analysis it is always the clinical phase of such studies that interests us most. Just how and where shall we use the facts resulting from the laboratory investigation; that is to say, the pharmacodynamic and the chemical study of these drugs?

It is probable that there is to-day no subject in ophthalmic science on which there is more diversity of opinion than that of which is the cycloplegic that stands for maximum of effect and minimum of irritation to the eye, minimum inconvenience to the patient and surgeon, and minimum period of incapacity to the patient. This would be opening up the whole question of the various mydriatics and their various methods of use by different workers, which is not my desire. Suffice it to say that semi-occasionally I use homatropin and infrequently I use atropin. In the last six years, however, in something like 2,000 cases of refraction in private work I have used a 1/10 per cent. solution of hyoscin hydrobromate ($\frac{1}{2}$ gr. to the oz.), containing cocaine also in the strength of 1/5 per cent., and not once have I seen a pronounced toxemia, by which I mean sufficient inconvenience of the patient to make him too uncomfortable to go home. In about one case in fifty there is rather marked flushing of the face, quickening of the pulse and some slight vertigo, not more, however, than I have seen a number of times with homatropin. This was in all probability due to the fact that the patient did not follow the instructions about pressing over the canaliculi five minutes after the drug was instilled. Neglect of this precaution invites toxemia with whatever mydriatic is used. The hyoscin has been used quite as freely in little children as in adults and never have I seen a pronounced general reaction in these little ones. It is my custom to have the patient have the solution instilled once or twice the evening before and twice the morning of the consultation. This is sometimes reinforced by another drop after the patient reaches the office. For office instillation the use of the solution is preceded five minutes by one drop

3. Incidentally it might be noted that in Merck's price list for October, 1906, under the price given for hyoscin hydrobromid, appears the statement that "Hyoscin (Merck) and its preparations are all obtained from hyoscyamus and not from scopolia."

of a 2 per cent. cocain solution, which is always warmed, as are the hyoscin drops also. Two such hyoscin instillations are made half an hour apart, and any time one to two hours after the first instillation the patient may be satisfactorily tested for errors of refraction in the vast majority of cases. A very small percentage (not more than 1 per cent. to 2 per cent.) will thus show that they need atropin. Accommodation sufficient for the purposes of all but the most exacting near work is generally re-established by the end of 48 to 60 hours. That is to say, that if a patient is measured on Saturday he may use his eyes somewhat for near work on Monday and pretty much as he is usually accustomed to on Tuesday.

There are those who like to give their patients a weak eserine solution to hasten the return of accommodation, but except under dire pressure I dislike exceedingly to do this because of my belief that much of the precious therapeutic action of the cycloplegic is thus done away with. Few patients are as busy or pressed for time as they think they are, and if the facts concerning their eyes are rightfully and tactfully put before them there are few who will not abide by their ophthalmic counselor's advice.

It is almost needless to say that I would be delighted to report every eye-strain patient's eyes under atropin because of its twofold action of complete cycloplegia and perfect rest to all the internal ocular structures. But as the tension of life in this year of grace 1907 makes it impossible to realize this ideal the search must be for the next best thing, and that, in my humble estimation, is to be found either in scopolamin hydrobromid in 1/10 per cent. solution, or, as I prefer, hyoscin hydrobromid in 1/10 per cent. solution.

It is always a matter for regret to have to admit that the number of cases submitted to experiment is so small as to leave room for doubt as to the accuracy of the conclusions drawn from the work. The foregoing work is, in a sense, open to this criticism, and yet cases suitable for this kind of experiment do not occur frequently, and even when found such patients are frequently unwilling to submit to the inconvenience of a repeated mydriasis, no matter how valuable the data that might issue therefrom. The claim is, therefore, made that the results herein set forth are entitled to consideration and may be accepted as working results until such time as some other worker by a larger series of cases may be in a position to rise and disprove them.

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DISCUSSION.

DR. ALBERT E. BULSON, JR., Fort Wayne, Ind., agreed with Dr. Reber that hyoscin is more effective than scopolamin as a cycloplegic. For the last four or five years he has used hyoscin almost exclusively as a cycloplegic and found it more reliable than homatropin and more evanescent than atropin. He did not concur in the statement that patients can use the eyes comfortably within forty-eight hours. The majority of his patients complain that accommodation is so paralyzed for seventy-two hours, and sometimes longer, that reading is an impossibility. Some patients even complain of the effect as late as the fifth day, but even this prolonged action, he said, is an advantage over atropin which generally lasts ten days to two weeks. Children are less susceptible to systemic effects of the drug, and in Dr. Bulson's experience they show toxic symptoms less often and to less extent than adults.

But, Dr. Bulson, said, it is absurd to think that toxic effects will not occasionally occur, notwithstanding the utmost caution. In an experience of several thousand cases in which hyoscin was employed, he has never seen any alarming symptoms, though frequently he noted toxic effects which war-

ranted careful observation of the patient for some hours. For this reason he is opposed to giving the patient a prescription for the drug. If unpleasant effects are to occur he prefers to have the patient in his office under observation, and thus be able to overcome any embarrassing complications which might arise. The strength of the hyoscin solution should never exceed 1 per cent. As a routine practice, Dr. Bulson uses it in the strength of 1/2 per cent. solution.

DR. S. D. RISLEY, Philadelphia, said that he was compelled to abandon the use of hyoscin many years ago, because of the severe constitutional effect. Other points which greatly interested him are the peculiar isometric properties of duboisin, homatropin, atropin and sulphate of hyoscyamin. While chemically indetical, they produce very different physiologic results, especially in the duration of the paralysis of accommodation.

There is frequently great difference in the results obtained by different specimens of the same drug, and when discussing the matter with a leading chemist Dr. Risley learned that there are curious differences in the alkaloids of belladonna and hyoscyamus due to different methods of manufacture. If extracted in the presence of an alkali, hyoscyamin becomes atropin. If extracted or placed in solution with too great heat, the physiologic properties are materially altered, and their peculiarity in polarizing light is changed.

DR. CHARLES A. OLIVER, Philadelphia, has had considerable experience in the experimental study of cycloplegics. For certainty of results he has found it necessary to obtain the same form of eye, the same character of subject, a proved variety of drug, the best of test-object, and to do the work under similar conditions. He made each series of experiments at never less than four to six weeks apart. He has no faith in the present test-type methods of experiment. His experiments were done with the needle-point method. Hyoscin was found to be toxic to the extreme. Clinically, Dr. Oliver prefers atropin in public work; using three drops of it in 4 grains to the ounce strength solution the day before and the morning of examination. In private work he employs scopolamin in one-drop dosage, of a one-grain strength, one hour before the examination. Homatropin, he said, is practically useless to bring out very fine degrees, such as 1/8 D.

DR. G. H. PRICE, Nashville, asked in what strength and with what frequency the homatropin was used.

DR. OLIVER replied, two, four, six, eight grains at intervals of five minutes. In some of the cases he found full cycloplegia, but more often ocular irritation to such a degree that proper subjective answers could not be obtained.

DR. ALLEN GREENWOOD, Boston, has used hyoscin hydrobromid in 1/2 grain to the ounce solution, applied four times, and on one occasion a young lady developed acute mania in the waiting-room. Another little girl was maniacal all the way home in the car. Following these two experiences he stopped the use of hyoscin. Dr. Reber's method of using the hyoscin, he thought, would probably obviate such trouble.

DR. S. L. ZIEGLER, Philadelphia, cited a case in which the druggist used hyoscin in substitution for homatropin, one grain to half a dram. It was instilled seven times within the hour, and the patient was prostrated, as in the case related by Dr. Greenwood. Dr. Ziegler has seen a hypodermic injection of 1/100 of a grain produce ataxic delirium. Nevertheless, he thinks that in the strength used by Dr. Reber it is possible to secure cycloplegia without having such toxic effects manifested.

DR. WENDELL REBER, Philadelphia, does not believe that even after homatropin is there total disappearance of cycloplegia for from three to five days. In the case of hyoscin or scopolamin it may run six or seven days. Relative disappearance is a different thing; the patient may be able to work much sooner than that. He never hesitates to order hyoscin in 1/2 grain to the ounce solution. By remaining below the toxic quantity one will get good cycloplegia without toxemia. Some of the worst cases of toxemia he has ever seen have resulted from atropin. Of course, it must be used with care so as not to get the drug anywhere but in the eye. Dr. Reber considers duboisin to be more toxic than hyoscin as used in everyday work. He uses hyoscin in his private and hospital work, and believes it to be the best cycloplegic