however, is a common occurrence in inflammatory states and cases of intraocular haemorrhage and thrombosis wherein pathological rises of tension are by no means unknown. It is to be remembered that in these cases the influence of the increase in colloids in raising the pressure level is increased by the obstruction to the free exit of fluid which the albuminous nature of the aqueous will bring about. Finally it is to be noted that the original cause of the entrance of colloid particles into the chambers of the eye is a dilatation of the capillaries involving an increase in the permeability of their walls; and thus we return again to our first consideration, the essentially important capillary circulation.

The remaining point to consider is the matter of changes in the volume of the contents of the globe, and among these the greatest interest centres round the changes which occur in the vitreous. The general appearance of a typical glaucomatous eye, with the anterior chamber shallow and the iris and lens pushed forward, strongly suggests that one of the commonest and most important changes which occur in this disease is an increase in the volume of the vitreous. The vitreous is a gel bathed in aqueous; its chemical constitution and its structure as seen under the ultra-microscope show that it is so. The main determinant of the volume of such a system is the amount of water which it retains in association with it—that is, the degree of hydration of its colloid particles. This question of the swelling of gels is an extremely interesting one, and, unfortunately, one about which little is known at present even in the domain of pure physical chemistry. We are working on it at the moment, but the experiments are long and take weeks of observation, and it is too early yet to dogmatize on the results. This much we know, however, that the pressures generated on occasion may be enormous; it is the same turgidity pressure which the Egyptians used to such good purpose in their gigantic building operations. They inserted dry wedges of wood into the crevices of rocks, and when they poured water upon them the swelling of the wood split the rock asunder. We are as yet unaware of all the factors controlling the swelling. One influence is a change in the reaction of the vitreous: within the limits compatible with life an increase of the pH causes an increase of turgidity pressure, while a decrease of pH has the opposite effect. The concentration of salts is another determining factor, and there are others about which we know less. Whatever the mechanism may be in clinical conditions, it is evident that pressures may be generated in the vitreous of sufficient magnitude to push forward the lens and the iris, to expel most of the aqueous, and to compress the uveal blood vessels to a degree which will strangulate the eye.

These, then, appear to be the main mechanisms whereby the intraocular pressure may be raised. When the pressure is raised the "pressure circulation" makes its influence more markedly felt, and by the expulsion of some of the aqueous the normal pressure equilibrium is still maintained. With the anterior chamber rendered shallow, however, the margin of safety is lowered and a comparatively small increase of pressure, one with which the normal eye could deal quite safely, becomes a source of real danger. When, in addition, the exit channels lose their efficiency, the danger becomes greater; small rises of pressure become cumulative and large rises lead to complete and sudden strangulation of the globe. Probably many influences may act, either together or severally, in obstructing these channels; the formation of peripheral synechiae, sclerosis of the pectinate ligament, the deposition of iris pigment in the meshwork of the filtration angle, a defective inward pull of the ciliary muscle, or the pressure and obstruction of a gradually growing lens—each or all of these may be present and obstruct the exit of fluid, but it seems obvious that in the majority of cases their influence is adjuvant rather than primary, consequential rather than causal.

It will be realized from what has been said already that the etiology of glaucoma is not to be sought in one direction alone. The rise of pressure which we call glaucoma is a symptom common to many clinical conditions; further, there are clinical conditions wherein many of the symptoms characteristic of glaucoma are present in which no rise of

pressure can be detected. It is easy to argue that in these cases rises of pressure may occur intermittently at times when they have not been detected, but this can hardly explain the fact that it frequently happens that the progress of symptoms does not by any means run parallel with the tension, and frequently continues after its efficient operative relief. If we admit that physico-chemical changes do occur in the vitreous in some of these cases, it does not seem improbable that they continue after the mere mechanical relief of tension. After all, the nerve processes in the retina are ultimately physico-chemical in nature, and it is conceivable that they also may be deranged coincidentally. There is a considerable amount of experimental evidence, for example, that scotomata can be formed by inducing retinal oedema, but this question raises matters upon which so little has been done that their discussion seems unprofitable at the present time.

Taking glaucoma, then, as a pressure symptom merely, I would suggest that the two main factors in its etiology are these: first, a derangement of the capillary circulation, involving a capillary dilatation, which produces a rise in capillary pressure, or an increased permeability of their walls allowing an excess of colloids in the fluids of the eye; secondly, changes of a physico-chemical nature in the vitreous. About the first we know little, but are rapidly learning more; about the second we know less, but are slowly finding out more. These two may act either alone or together, and their effectivity in causing a permanent rise of pressure depends directly on the efficiency of the drainage channels in the region of the angle of the iris.

MERCUROCHROME 220 SOLUBLE.

BY

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AND

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IN 1920 E. C. White¹ obtained from dibromo-fluorescein and mercuric acetate an insoluble amorphous substance which he regarded on analytical grounds as dibromo-hydroxymercuri-fluorescein. He also analysed some commercial specimens of its di-sodium salt, "mercurochrome 220 soluble," obtaining results which differed considerably from the theoretical values for the formula:

Allowing for the water content of his samples, the agreement was better, but it is obvious that slight modifications in the method of manufacture might lead to the presence of one or more of the following impurities: (a) dibromo-fluorescein, (b) dibromo-di-hydroxymercuri-fluorescein, (c) mercury salts, and (d) sodium acetate. Contamination with appreciable quantities of (a), (b), or (c) might considerably modify the therapeutic properties of the drug (cf. Macht and Harden²). Elementary analysis affords the only criterion of purity for a non-crystalline substance of this type, and mercury determinations alone are not sufficient for this purpose, since, for example, the presence of (b) or (c) might be masked by that of (a) or (d). Accordingly it became of interest to examine a number of commercial samples of mercurochrome 220 more thoroughly, in order to determine first how nearly they approach in composition to the above formula, and, secondly, whether the purer specimens are pharmacologically superior to the others. The analytical results given in Table I for what purport to be four samples of the same compound are surprising. A, B, and C were obtained from ordinary trade

sources, whilst D was manufactured by the published method by Messrs. British Colloids Limited.

TABLE I.

Mercurochrome 220 soluble.	Found.				Calc. for dry material.		
	Hg%*	Br%†	Acetate as C ₂ H ₄ O ₂ *‡	H ₂ O%‡	Hg%	Br%	C ₂ H ₄ O ₂ %
Theoretical for C ₂₀ H ₈ O ₆ Br ₂ Na ₂ Hg					26.7	21.3	0.0
White (loc. cit.) ...	23.0				24-25		
A	37.4	10.4	6.9	8.5	40.9	11.4	7.5
B	24.1	17.4	1.2	11.3	27.2	19.6	1.3
C	28.2	23.0	2.4	10.5	31.5	25.7	2.7
D	23.2	18.8	1.5	10.5	25.0	21.0	1.6

* By White's method (loc. cit.).

† By the Carius method.

‡ Loss of weight at 110° and 15 mm. pressure. Since all samples lost a trace of mercury under these conditions, the water contents and, in consequence, the values for the composition of the dried products are probably rather high, but, in view of the relatively large discrepancies observed, this is of little importance.

The high acetate content of A indicates that the insoluble intermediate from which it was prepared has been insufficiently purified by washing, while the high mercury and low bromine values show that approximately 40 per cent. of (b), (c), or similar impurities must be present. C, which contains, in addition to a rather large amount of acetate, more than the theoretical amount of both bromine and mercury, was probably prepared from an impure dibromofluorescein containing tetrabromo-fluorescein. Its composition could be imitated by adding a mixture of tribromohydroxymercuri-fluorescein and dibromo-di-hydroxymercuri-fluorescein to mercurochrome 220. On the other hand, samples B and D are fairly pure. Allowing for the moisture and small quantity of acetate present, D has nearly the theoretical composition.

Young, White, and Swartz,² in their original paper on mercurochrome, stated that 10 mg./kg. invariably killed rabbits in twenty-four hours, and that *post-mortem* examinations showed no gross lesions; 5 mg./kg. caused albuminuria lasting about a week. On the other hand, 10 mg./kg. were well tolerated by dogs. In later papers it is stated that this toxicity to rabbits is about the same as for men.^{3,4} Other observations⁵ have been made both on animals and on men suffering from gonorrhoeal urethritis, from which the conclusions are made that the intravenous injection of mercurochrome with glucose is less toxic than mercurochrome alone, and that the therapeutic efficiency is either not affected or is even enhanced. Mercurochrome glucose therapy is strongly advocated in the treatment of all types of genito-urinary infection.* Macht and his co-workers point out that mixtures of mercurochrome with glucose soon undergo a change with the precipitation of mercury, and although they agree that the glucose renders the mercurochrome less toxic, they insist that the mixture should be made immediately before injection.⁷ The same writers give evidence to show that the toxicity of mercurochrome 220 soluble is lower than has been stated, the average lethal dose for a rabbit being about 30 mg./kg. They regard their figures as due to the elimination of impurities by improving the method of production.

Clinical experience of the intravenous injection of mercurochrome in man during the past four years has impressed the fact upon one of us that a concentration of 1 per cent. frequently gives rise to symptoms of mercurial poisoning, as shown by acute colitis and diarrhoea with pinkish stools, and that comparable doses of 0.4 per cent. solution are relatively free from this objection. The present experiments were undertaken because our attention was drawn to the fact that certain samples of mercurochrome obtained in the open market were more toxic than others.

In the following toxicity experiments the injections were always made as a 0.4 per cent. solution. Young adult rabbits, weighing about 1.5 to 2 kilograms, were selected

for the toxicity tests; injections were made directly into the ear vein of doses varying from 10 to 27 mg. or more per kilogram of body weight.

The results at first obtained were somewhat discordant, since doses up to 25 mg./kg. of body weight were well tolerated by some animals, while similar or even smaller doses proved fatal in others in from five to ten days. The results of some experiments tabulated in ascending doses of the drug make this point clear.

TABLE II.

Rabbit No.	Body Weight in Grams.	Sample of Mercurochrome 220.	Dose in mg./kg. of Body Weight.	Loss of Weight in Grams during following 48 hours.	Result.
1	3,000	A	10	Nil	Recovered.
2	2,400	B	15	100	Recovered.
4	2,200	A	18	400	Died (10 days).
5	2,000	B	20	300	Recovered.
6	2,300	D	20	200	Recovered.
7	1,850	A	22	200	Died (5 days).
9	1,900	A	25	300	Died (5 days).
10	1,750	D	27	250	Recovered.
17	2,500	D	30	300	Recovered.
18	2,400	D	50	400	Died (2 days).

The *post-mortem* appearances observed in animals dying shortly after the intravenous injection of mercurochrome 220 were quite characteristic, and in addition to pinkish staining of the tissues and organs, especially the lungs, there was a marked excess of fluid, rose-pink in colour, in the peritoneal and pleural cavities, the intensity of colour being in inverse ratio to the length of time that elapsed between injection of the drug and death.

These results suggested that the "source of origin" of the drug was of more importance than the magnitude of the dose given, within certain limits. At this stage the chemical constitution of several of the commercial brands, as already detailed, became available, and on reading the results of the toxicity tests in the light of this information it was seen that toxicity depended, in part at any rate, upon the amount of mercury in the mercurochrome. This point is well shown in Chart A (showing experiments with sample A), and in Chart B, in which sample D was used.

CHART A.

The same dose—that is, 25 mg. per kilogram of body weight—was used for each of six normal animals of nearly equal weight.

The results shown in tabular form may be summarized by saying that four of the rabbits in Set A died within nine days with typical *post-mortem* appearances; the rabbits in Set B showed in most cases similar initial loss of body

weight, but were otherwise unaffected, and were alive and well at the end of six weeks' observation, with but one exception, which was killed accidentally.

CHART B.

Repetitions of the series of experiments set out in Chart B were made, and established the fact that the young adult rabbit would tolerate a dose of 25 mg./kg. of body weight of Sample D when the concentration of the drug did not exceed 0.4 per cent. Further experiments were

CHART C.

carried out to investigate the effect of employing the same dose—namely, 25 mg./kg.—but increasing the concentration of mercurochrome to 1 per cent. solution. A typical series of experiments is set out in Chart C, which shows clearly the marked drop in body weight (in one instance amounting to 650 grams); this was associated with obvious malaise within forty-eight hours after injection, and later a fatal termination. These observations appear to support the clinical statement referred to, that 0.4 per cent. was to be preferred to the 1 per cent. concentration for intravenous injection.

INHIBITION COEFFICIENT.

At this stage tests were begun with Sample D to determine the inhibition coefficient—that is to say, the percentage of the drug which, when present in the nutrient medium, is sufficient to prevent the growth and multiplication of the test bacterium. The test organisms employed were *B. coli communis* isolated from a normal stool, and a highly virulent *Streptococcus longus* (*haemolyticus*) isolated from a fatal case of septicaemia following an infected insect bite. In the case of *B. coli* a solution of 1 part mercurochrome in 3,500 nutrient broth (equivalent to 0.002 per cent. mercury) was the smallest quantity inhibiting growth, whilst, with the more sensitive streptococcus, growth was inhibited by a 1 in 8,000 dilution (=0.0004 per cent. mercury).

THERAPEUTICAL OBSERVATIONS.

During the past few months, among both hospital and private patients, an unusually large number of cases of pyrexia have occurred, which when first seen were of unknown origin. These cases presented the clinical picture of septicaemia, and in a number it was decided to employ mercurochrome. For this purpose Sample D was employed, because analytical results conformed most closely to the theoretical constitution.

In many of these cases we failed to establish bacteriologically the diagnosis of septicaemia based on clinical appearances. For example, in one instance—a schoolboy, aged 13—*Streptococcus longus* and *Staphylococcus aureus* were isolated from the pus of a suppurating nodule on the shin following a septic corn, which was the starting point of the illness, but no laboratory evidence could be obtained to show that either of these organisms had entered the blood stream. The result of the injection of mercurochrome in this case was dramatic. The symptoms immediately disappeared and the patient made an uninterrupted recovery.

In the case of another schoolboy, aged 14, a "blood blister" on the heel became septic, and on the third day rigors and a temperature of 104° F. occurred. On the fifth day a spreading cellulitis of both legs and the left hand and wrist necessitated incisions; an antistreptococcus serum was injected, without improving the condition. Bacteriological investigations were made on the sixth day and showed a growth of *Staphylococcus pyogenes aureus* from the various incisions, and a blood culture showed the presence of the same organism in the circulating blood. Mercurochrome 15 c.cm. was injected after the withdrawal of the blood for culture, and further 10 c.cm. doses were injected on the eighth, tenth, twelfth, and fourteenth days. The temperature fell to a lower level, but the patient's condition became very grave. Cultures of blood made on the thirtieth day were sterile. Transfusion with Group IV blood was performed on the thirty-third day, and at the same time a specimen of blood was taken for cultural purposes; this also was sterile. A further transfusion was undertaken, but the patient gradually sank. In this case mercurochrome would appear to have dealt effectively with the general septicaemia, although it did not prevent a fatal termination.

From the remaining cases, three of puerperal sepsis and one of mastoid disease have been selected for description. In these the septicaemic nature of the disease was demonstrated by the isolation of the responsible micro-organism from the peripheral blood; and the duration of the infection was sufficiently short to permit reproduction of the temperature charts, in which the arrows indicate the injection of mercurochrome (M) or anti-streptococcal serum (S).

CHART D.—D. M.

A married woman (D. M.), aged 32, required forceps delivery after a prolonged labour. Rigor and a temperature of 104° F. followed on the ninth day of the puerperium, when 20 c.cm. of an antistreptococcal serum (polyvalent) was injected, without producing any fall of temperature. On the fourteenth day a blood culture produced a growth of *Streptococcus longus* (*haemolyticus*); 15 c.cm. of mercurochrome was injected at the time the blood was withdrawn. The temperature fell to normal on the following morning. After forty-eight hours the temperature rose again (to 102° F.); a second dose of 15 c.cm. mercurochrome was given, and was followed by a fall of temperature to normal on the nineteenth day, after which convalescence progressed uninterruptedly.

In another married woman (M. T.), aged 27, labour was uncomplicated; she was attended by a midwife. On the third day of the puerperium there occurred a rigor with a temperature of 106° F.; a blood culture gave a heavy growth of *Streptococcus longus* (*haemolyticus*). On the fourth day 10 c.cm. of mercurochrome was injected intravenously; this was followed by a fall of temperature on the following day. On the sixth day a second dose of 10 c.cm. of mercurochrome was injected. On the eighth day there was a sudden rise of temperature to 104° F., at which point 20 c.cm. of mercurochrome was injected. The temperature then fell steadily and was normal on the nineteenth day.

Pyrexia of unknown origin occurred in an unmarried woman (N. W.), aged 28; the clinical symptoms suggested typhoid, but examination of the faeces and urine gave negative results. The serum agglutination tests against typhoid and paratyphoid bacilli were negative also up to the twenty-first day. A blood culture on the twenty-seventh day showed a heavy growth of *Streptococcus longus* (*haemolyticus*) within forty-eight hours. On the twenty-ninth day 20 c.cm. of mercurochrome was injected intravenously, followed on the thirtieth day of illness by 35 c.cm. of mercurochrome.

chrome, immediately after the withdrawal of 10 c.cm. of blood for culture purposes. Of this culture three tubes only, containing 2 c.cm., 2 c.cm., and 2.5 c.cm. respectively of blood, showed *Streptococcus longus* (*haemolyticus*) after seventy-two hours' incubation. On the thirty-third day mercurochrome (21 c.cm.) was again injected. A blood culture on the fortieth day was sterile. On the next day the temperature fell to normal and did not rise again.

A girl (D. L.), aged 12, contracted measles at school; eight days later she complained of earache, which passed off. On the fifteenth day of illness the temperature suddenly rose to 103° F., with return of the earache. On the seventeenth day the tympanum was incised and a radical mastoid operation was performed. On the twentieth day a rigor occurred and the temperature rose to 103° F.; 20 c.cm.

CHART E.—M. T.

CHART F.—N. W.

CHART G.—D. L.

of a polyvalent antistreptococcal serum was injected without obvious improvement. On the eighteenth day a blood culture showed a heavy growth of the *Streptococcus pyogenes longus* (*haemolyticus*); 15 c.cm. of mercurochrome was injected immediately after the blood had been withdrawn from the vein. On the twentieth day 12 c.cm. of mercurochrome was injected, on the twenty-first day 10 c.cm., and another 10 c.cm. on the thirtieth day of illness. The temperature had become normal on the thirty-first day, and convalescence thereafter was uninterrupted.

The general impression produced during the use of mercurochrome D was that its therapeutic activity was similar to other types of mercurochrome used during the previous four years, but that it was distinctly less toxic. It is, of course, impossible to discount entirely the operations of the long arm of coincidence. In dealing with clinical evidence of the type here presented it is equally impossible to affirm that no other treatment would have been equally effective, or, indeed, that the patients would not have done equally well without any treatment. But controlled experiments on animals have made it clear that

mercurochrome can effect a cure in a considerable proportion of cases.

We are, of course, aware that it has been stated that animals and men who have received mercurochrome exhibit no bactericidal properties in the blood and bile. This suggests that the action of this substance is not a simple effect on the micro-organisms, but that it follows the law of chemotherapy, in that it acts only through the body tissues. Bayer 205 has little apparent action on trypanosomes *in vitro*, though it may suffice to cure animals and men suffering from *T. gambiense*.

CONCLUSIONS:

1. The various specimens of mercurochrome on the market differ markedly in their chemical composition.
2. Toxicity appears to bear a direct relationship to purity of composition.
3. The nearer mercurochrome approximates in its analytical results to its known chemical constitution, the better the preparation as regards therapeutic efficiency and low toxicity.

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ARTIFICIAL HELIOTHERAPY IN THE ROUTINE TREATMENT OF SURGICAL TUBERCULOSIS.

BY

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WITHIN the past decade much attention has been paid to the curative effect of sunlight, and more especially to the effect of the ultra-violet rays, in many kinds of disease; rickets, marasmus, skin conditions, neurasthenia, rheumatism, hay fever, surgical tuberculosis, and a host of other conditions have been described as being amenable to treatment by heliotherapy. Indeed, a reviewer of a recent publication on this subject says, "apparently there is hardly any condition for which they [the authors] fail to recommend ultra-violet light." Rollier has been the chief advocate of heliotherapy as a method of treating surgical tuberculosis, his results in alpine sanatoriums having been very successful. Owing to the lack of natural sunshine in this country artificial heliotherapy has been strongly urged as a useful and practical substitute, and many hospitals have installed artificial sunlight lamps.

Such an installation was introduced in Edinburgh City Hospital in the latter part of 1924, and since then all cases of surgical tuberculosis in which there was no definite contraindication, such as pulmonary lesions or intolerance to light, have had routine heliotherapy.

Apart from the use of heliotherapy, all the cases have been treated in the same manner as previously. The

treatment of the local lesions consists in putting the part as completely at rest as possible. In the case of bone and joint infection this is attained by splinting; in the case of abdominal tuberculosis and other gland lesions where such anatomical rest cannot be secured, physiological rest is as far as possible obtained. In all cases the general health of the patient has been thoroughly investigated; rest in bed is enforced during the earlier part of treatment, all foci of infection are sought out and, if possible, eradicated. The open-air life of a sanatorium is insisted on, and the wards are so constructed that whenever possible the patients are wheeled out in their beds into the open.

The results of treatment by heliotherapy in cases of surgical tuberculosis have been gauged hitherto chiefly by the clinical observation of individual cases, but statistics of larger series of cases are now available.

I have attempted in the following statistics to tabulate the results of the treatment of surgical tuberculosis in the Edinburgh City Hospital, and to compare these with the results obtained before the introduction of heliotherapy.

The method of heliotherapy employed has been general exposure to the rays from a carbon arc lamp—using tungsten-cored carbons. The patients commenced with an exposure for ten minutes, and this was increased daily by ten minutes until a daily exposure of two hours was being received. With this routine very few patients have come under my notice on whom the treatment had any deleterious effect, such as skin irritation, gastro-intestinal upset, rise of temperature, loss of sleep, or general malaise. In a few