are accidental and not the cause of the affection. He believes that the proliferation of the connective tissue from the adventitia is the consequence of the irritation, produced by chemical and toxic substances in the vitreous.

In both our cases, hemorrhages in the retina were insignificant, a rather small spot being present on the surface of the new formed membrane of the first and several round ones on the

retina of the second, not dissimilar to those of an ordinary retinitis. None were observed in the vitreous, altho we had the opportunity to examine the patients repeatedly for a long period. This fact renders the two cases which we have reported very interesting, as it confirms the opinion of those writers who deny absolutely that hemorrhages precede and are the cause of the proliferation of the retina.

SOME FACTS ABOUT SALICYLAT THERAPY.

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This paper summarizes observations bearing on the way in which salicylates, and drugs having similar effects, produce benefit in ocular inflammations. Practical points in the use of this class of drugs are given. It is based on work done in the Department of Ophthalmology of the University of Nebraska Medical College. Read before the Colorado Congress of Ophthalmology and Oto-Laryngology, July, 1922.

In spite of the undoubted value of the salicylates in ocular diseases, their use is still based on almost purely empiric grounds. Many theories have been proposed as to their mode of action, and some careful investigations have been carried out. While this work has not shown any one theory to be correct, it has incidentally brought to light some facts about the drug, which should not be without interest to clinicians.

In another paper¹, I have discussed these theories of the general action of the drug, but they may be briefly summarized here.

The first explanation that occurs is, that the drugs may be bactericidal in their effect, or inhibit bacterial growth. Sodium salicylat and acetylsalicylic acid, however, require concentrations of 1:250 or more to inhibit bacterial growth, and much greater concentrations to kill bacteria. Since these concentrations could never be obtained in the living body, it is evident that the effect of the drug is not directly bactericidal.

Salicylic acid inhibits growth at 1:1000 and kills bacteria at 1:300, but since it is a severe local irritant, it is not possible to secure such concentrations by giving the drug as such. It

was supposed, however, by Binz² and others, that the free acid might be split off from its salts in the tissues; and especially in inflamed tissues where the CO₂ tension is abnormally high. Other work, however, by Feser and Friedberger³, Hanzlik⁴, and recently by Boots and Cullen⁵, has shown that it is impossible to recover free salicylic acid from blood or any body tissues, whether inflamed or not, so that the free acid can play no part in any bacterial effect. Animal inoculation experiments have been no more successful. Work by Davis⁶ and Boots and Swift⁷ has shown no difference in the incidence of arthritis in inoculated animals with or without sodium salicylat, tho the latter workers found much clearer joint fluid in animals getting the drug. Infection occurred, but the reaction was much milder than in control animals.

Campbell⁸ observed leucocytosis after the drugs, and ascribed their effects to this increase in the body's defenses. It seems to me, however, that the leucocytosis was due to the infection rather than the drug in his cases; since I have observed⁹ cases of uveitis with blood counts before and after the drug was started, and noted no significant changes in the blood picture. Nor

was any change noted in the blood counts of animals getting the drug. So that it seems doubtful if leucocytosis plays any part in the action of the salicylates. H. Gifford¹⁰ believed Oltramare's theory to be the most acceptable. This assumed that the general vasodilatation caused by the drug produced a compensatory depletion of the previously engorged vessels in the inflamed part. As far as I know, there is little evidence for or against this, except the clinical fact that such general vasodilatation and local depletion does occur. A related explanation is that of Hanzlik¹¹ "that the benefit to the joints may possibly be attributed to the local circulatory effects, which facilitate the interchange of inflammatory products."

In using the salicylates, it is becoming generally recognized that large doses must be given to secure the desired effect. H. Gifford¹² was the first ophthalmologist to use anything like the present large doses in ocular affections, and his dosage for sodium salicylat, one grain per pound of body weight per day, has proven a convenient one to many clinicians.

One reason for the necessity of large doses is the rapidity with which the drugs are excreted by the kidneys. Salicyl is found in the urine within five to eight minutes after a dose by mouth. Hanzlik¹³ has shown, that the excretion continues for three to four days after a dose, the greater part is recovered in the first ten to twenty hours. Thus to produce any continued concentration in the blood or tissues, the doses must be large and frequent.

In considering the possible toxic effect of large doses, experimental work points to the kidneys as the organs most likely to suffer damage. Hanzlik¹⁴ has shown that such doses produce severe nephritis, often fatal, in animals; and that ordinary therapeutic doses caused the almost constant appearance of casts, leucocytes and albumin in humans. No serious effects were observed, but the albuminuria persisted for some time in a few cases. I have seen rabbits, and especially cats, develop fatal nephritis from

moderate doses. In spite of these findings, we have never seen a clinical case of human nephritis develop during salicylat therapy.

In some obstinate cases of uveitis, the congestion returns as soon as the drug is stopped, so that we often give sixty to ninety grains a day for periods of two to six months or even longer. One case of sympathetic ophthalmia has taken three hundred to four hundred grains of sodium salicylat per week for the past seven months, and is in perfect health. Another case of sympathetic ophthalmia developed scarlet fever, but the large doses were continued with no evident damage to the kidneys. Clinical experience, therefore, leads us to believe that these urinary changes, which are unquestionably found, if looked for, are temporary and usually of no consequence. It would seem prudent, however, to examine the urine of all cases before starting the drug, and if albumin is already present, to choose a drug less likely to harm the kidneys.

Clinicians still differ as to the use of sodium bicarbonat to prevent toxic symptoms. Ehrmann found that its only effect was to increase the rapidity with which the salicyl was eliminated, which would tend to lessen the effectiveness of the drug. Hanzlik found no such effect, nor any effect in lessening renal irritation. We have found it of no value in lessening gastric disturbances from sodium sayicylat, which is to be expected, as this is a neutral salt. Cincophen and acetylsalicylic acid, however, it probably helps convert to the less irritating salts. We do not use it with sodium salicylat, but do with cincophen.

As to the more generally known toxic symptoms, ringing in ears, slight nausea, and malaise occur fairly often, but are no indication for stopping the drug if it is still needed. Depressing effects on the heart may occur, but usually only with enormous doses, and their importance has been overemphasized, especially for aspirin, which is only slightly more toxic than sodium salicylat. I have never seen cardiac decompensation result from either

drug. Occasionally delirium follows large doses, and it may be alarming. Such cases are rare, however, and usually depend on contributing circumstances. They should be watched for, especially in extreme old age.

If vomiting occurs, rectal may be substituted for oral administration. Sixty grains of sodium salicylat may be given by high enema two to three times a day, and this is usually well absorbed. Recently, instead of this, I have been substituting cincophen or atophan for the salicylates. Cincophen, and its derivative, neocincophen, appear to offer almost perfect substitutes for the salicylates, where for any reason these cannot be given. Cincophen is phenyl cinchoninic acid. Atophan is the trade name originally applied to the same product, because of its supposed effect on gouty tophi. Neocincophen is the methyl derivative of cincophen. Chemically, these drugs are not very close to the salicylates, but pharmacologically their effects are almost identical. Hanzlik and Scott¹⁵ have investigated the effects of these drugs in rheumatic fever. They found both as efficient as the salicylates in lowering fever and stopping pain, tho larger doses of neocincophen were required. The urinary changes after cincophen were much less marked than with the salicylates, and still less marked after neocincophen. Other toxic symptoms similar to those after the salicylates were observed, but these were seldom severe. Epigastric pain was a symptom peculiar to cincophen patients. Chace, Killian and Myers¹⁶ found toxic symptoms much less marked than with the salicylates.

I can attest to the occurrence of epigastric pain after cincophen, tho it was never severe, and in my experience nausea has been much less frequent than with the salicylates, and vomiting has not occurred once. Patients whose stomachs will not tolerate salicylates, usually take cincophen with little or no discomfort. Besides this, I have seen a number of cases of iridocyclitis which failed to respond to large doses of sodium salicylates, but which cleared up promptly on cincophen. I am at present seeing two such

cases, whose congestion returns in about forty-eight hours after cincophen is stopped, but disappears at once as soon as it is resumed in small doses. (30 grains a day.)

As to the dosage, Hanzlik gave 150 to 195 grains of cincophen, and 165 to 240 grains of neocincophen before results were obtained. Chace, Killian and Myers gave 50 to 100, and in one case 200 grains of neocincophen daily, without marked toxic symptoms. I start on 100 grains in severe cases, (80 in less severe) and cut down after two or three days to 80 and then 60 grains a day. It seems best, usually, to keep up doses of 30 to 45 grains a day for some time after the eye is quiet. The principal objection to these drugs is their price. Chiefly for this reason, sodium salicylat is usually used where it is well borne. If the usual one grain per pound per day is not effective, it should be pushed to 175 or 200 grains a day, and this will often bring a prompt response.

In using one of these drugs, in nearly all cases of nonspecific iritis, iridocyclitis, and optic neuritis, congestion after cataract extraction, and of course sympathetic ophthalmia, the causes of these conditions are not lost sight of, and are eliminated as soon as found. The drugs are of immense service in these cases, however, by lessening the reaction and preventing permanent inflammatory changes until the effect of causal treatment can be secured.

Some laboratory work undertaken this year is far from finished, and has proven nothing definite as to the action of the salicylates. It has, however, brought out some facts as to the occurrence of salicylat in the eyes, which I had not previously known. Whitham¹⁷, in 1913, experimented on the occurrence of salicyl in the aqueous, after the injection of several salicylat derivatives. Tests for salicyl could be obtained in the aqueous of rabbits 4 to 6 hours after the drugs were given by mouth. The strongest tests were given with urotropinsalicylat after which formalin was also found in the aqueous. A slight increase in the amount of salicyl was

noted after hot packs were applied, more after a previous paracentesis, and a considerably greater increase after drops of 10 per cent dionin and subconjunctival injections of salt solutions. Aqueous obtained in one of these tests apparently inhibited the growth of pneumococci in the test tube. Whitham's estimations of the amount of salicyl were not quantitative but only comparative.

Working with the quantitative method of Hanzlik, I attempted to find whether any greater concentration of salicyl was present in an inflamed than in a normal eye, and whether free salicylic acid was present in either. Sodium salicylat was fed to rabbits and cats by stomach tube, and one eye was injected with a virulent culture of staphylococcus. The aqueous of each eye was tested from time to time, and finally the animals were sacrificed, each eye extracted and the salicyl estimated. The amounts present in the blood were also estimated at as nearly as possible the time when the other specimens were obtained. No free salicylic acid was ever obtained from either inflamed or normal eyes. No greater concentration of salicyl was found in the inflamed than in the normal eyes. In fact, in the few experiments which were completed, the reverse was true.

It was interesting to know the rapidity with which salicyl appeared in the aqueous after a dose of sodium salicylat by stomach tube. It was detected once in twenty-five minutes and usually in thirty-five to forty-five minutes. After forty minutes, enough was usually present to be estimated quantitatively. No important differences were noted in this respect between cats and rabbits. After a dose of 15 grains to a rabbit, salicyl could be detected in the aqueous after twenty hours, but not after twenty-four hours.

In two animals, the various parts of the eye were separated, weighed, and extracted separately. In both cases, most of the salicyl was found in the aqueous and vitreous, there being none in the lens, and only a small amount in the uveal tract and in the

corneoscleral coat. Concentration in the aqueous and vitreous were about the same. In one human case, getting ordinary doses of sodium salicylat, I obtained a very strong test for salicyl with the aqueous. In another case, tests were negative on two occasions.

In animals, the concentration in the aqueous, after repeated doses, reached 1:3600 to 1:1250. In the whole eye by weight, it reached 1:5900 to 1:4100. In the one rabbit whose aqueous showed salicyl in a strength of 1:1250, the concentration in the pericardial fluid was 1:5000, while it was only 1:17,500 in the blood. In four other rabbits and one cat, there was also noted a greater concentration in the aqueous than in the blood, and in two of these, the difference was very marked. These results were unexpected and are not in agreement with the work of others on joint fluid. But an accumulation of the drug in a relatively stagnant serous cavity from the circulating blood, is not unthinkable. (I would like to have the opinion of someone who knows all about the physiology of the intraocular fluids as to this possibility.)

It was found that the method used for extracting salicyl from such small amounts of blood and tissues involved considerable loss, and Dr. A. L. Rubnitz and I are now working out what we hope may be a more accurate method. Such large differences as were observed in a few cases, however, can hardly be ascribed to the method. And the fact that such concentrations of salicyl can be obtained in the eye, even if they can never be bactericidal, may help to make more intelligible whatever effect the drugs do have. From present indications, it would seem that their action will be found to involve some of the intimate facts of metabolism, altho their vasomotor effect is also to be remembered. In any event, the salicylates, together with cincophen and neocincophen, are practically unique in their effect on local inflammation, so that they may be called the antiphlogistic drugs par excellence.

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OCULAR MANIFESTATIONS IN A CASE OF HYPOPHYSEAL SYPHILIS.

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In this case, with marked Fröhlich's syndrome and abnormal sugar tolerance, there was marked choking of the discs and contraction of the visual fields. Wassermann reactions were negative, and no cause was discovered for the ocular condition. Decompression to save the sight showed no intracranial pressure. Prolonged thyroid and pituitary feeding were attended with improvement of vision. Fluid from the ventricles gave a Wassermann "4 plus". Antisymphilitic treatment was pushed, and brought the eyes to normal. Read before the American Ophthalmological Society, May 1922.

The clinical aspect of a case of hypophyseal disease with primary or neighborhood syphilitic manifestations is here reported, mainly on account of the comparative infrequency of the complication, and the difficulties encountered in arriving at a definite conclusion.

Cases of acquired or congenital syphilis of the hypophysis are mentioned in the literature of neurosurgery, and obviously most of those cases were found, or at least the clinical diagnosis confirmed, by autopsy. De Schweinitz's recent article upon a similar topic reports much of the recent literature, to which the reader is referred.

History. An unmarried woman, age 24, was first seen April, 1921, with defective vision as the principal complaint, which dated back about two months. There were other important points in the history, which should be here recorded: (1) an increase of weight, that is a gain from 190 pounds

at the age of 18, to the present weight of 255 pounds; (2) polyuria, as long as she could remember; (3) polydipsia since childhood; (4) bitemporal headaches; (5) irregular and scant menstruation for five years, at which time she began to put on excessive weight; and (6) anaphrodisia.

The other important extracts from the history are taken from the careful notes made by Doctor Chas. E. Dowman and Doctor J. E. Paullin, consultants in the case.

Family history was negative for tuberculosis, cancer and neurologic diseases. The father, mother and five brothers were living and well. Two children died in infancy. The mother miscarried at a four months' pregnancy.

Except for diseases of childhood, the patient's health was always good. There was a history of scarlet fever, complicated with a right otitis media, which permanently impaired the hearing. Five years ago she had fainting