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ON THE ACTION OF ERGOTOXINE; WITH SPECIAL REFERENCE TO THE EXISTENCE OF SYMPATHETIC VASODILATORS.

By H. H. DALE.

(From the Wellcome Physiological Research Laboratories, Herne Hill.)

THE observation, that small doses of adrenine have frequently a depressor instead of the more familiar pressor action, is probably common to the experience of many who have had frequent occasion to observe the action of varying doses of this substance on the blood-pressure of carnivora. Several observers have recorded the phenomenon incidentally (Cushny[1], Elliott and Durham[2], Chiari and Fröhlich[3]). Cannon and Lyman[4], who, in a recent paper, discuss the meaning of the effect, and emphasise its importance in the regulation of blood-pressure under normal conditions, quote a number of other publications in which it is mentioned. They show clearly that it is not due to decomposition products or other impurities, but is a vasodilator effect of adrenine itself, and regard it as analogous to the vasodilator action produced, by any dose of adrenine, after ergotoxine has been given. This has always been my own assumption, when I have observed this normal vasodilator effect of adrenine, but I have been inclined to interpret the somewhat variable effect in the normal animal in the light of the relatively constant effect seen after ergotoxine. Cannon and Lyman appear to argue in the reverse direction, and, finding that the vasodilator action in the normal animal is only obtained when the arterial tension is above a certain critical level, conclude that the action of ergotoxine is simply to raise the arterial tension above this critical level, when it has been otherwise depressed. Such a rise of arterial tone is undoubtedly a factor in the apparent effect of small doses of

[1] This *Journal*, XXXVII. p. 137. 1908.
[2] *Ibid.* XXXIV. p. 494. 1906.
[3] *Arch. f. exp. Path. u. Pharmakol.* LXIV. p. 214. 1911.
[4] *Amer. Journ. of Physiol.* XXXI. p. 376. 1913.

ergotoxine, such as Cannon and Lyman employed; but, as an explanation of the reversing effect on adrenine action of full doses of ergotoxine, I believed that I had fully considered and disposed of this possibility in my first paper on the subject (cf. This *Journal*, XXXIV. p. 201. 1906 "Another...inconsistent"). As the point seems still in doubt, however, and as Cannon and Lyman suggest that I have not appreciated the significance of the critical level of pressure, it seems desirable to emphasise my previous statement by recording the details and illustrating the result of an experiment, in which an adequate dose of ergotoxine lowers the blood-pressure, and at the same time reverses the pressor action of adrenine. Cannon and Lyman attribute much significance to their failure to produce a fall of blood-pressure by stimulation of the splanchnic nerves after excluding the supra-renal glands from circulation. The recent work of Elliott and others, on the secretion of adrenine in response to stimulation of these nerves, made it further of interest to re-examine the effect of splanchnic stimulation after ergotoxine, in the absence of the supra-renal glands. I take the opportunity, therefore, of describing experiments on this point, and of quoting an experiment showing the effect of ergotoxine on the response of the ferret's uterus, which further illustrates the inadequacy of Cannon and Lyman's conception of the action of this alkaloid.

(1) *The vasodilator action of adrenine after ergotoxine.*

I have previously pointed out that, though small doses of ergotoxine have a primary stimulant action on the plain muscle of various organs, including the arteries, the effect soon passes over into a paralysis of motor sympathetic effects, so that normal tonic impulses to the arteries are blocked. After a certain low limit of dosage has been passed, therefore, further administration of ergotoxine merely hastens the fall of the arterial tone, to a level below that at which it originally stood.

Exp. 1. (Cf. Fig. 1.) The spinal cord of a cat was cut at the level of the second vertebra and the brain destroyed, as described elsewhere[1], the animal being fully under ether until the destruction of the brain was completed. The arterial pressure was recorded from a carotid artery, and injections made into a femoral vein. With the blood-pressure at 130 mm. 0·025 mgm. of adrenine was injected. The upper curve in Fig. 1 shows the resultant rise to 235 mm. Injection of 1 c.c.

[1] This *Journal*, XLI. p. 22. 1910.

of an extract of ergot, which was being tested, and which contained approximately 1 mgm. of ergotoxine, caused a large rise of blood-pressure. As this was subsiding 4 mgms. and then 5 mgms. of ergotoxine phosphate were injected, making about 10 mgms. in all. Each of these later doses caused a temporary dip in the curve, which otherwise fell smoothly. When it had reached 110 mm. and was declining more slowly, 0·1 mgm. of adrenine was injected, and produced the practically pure vasodilator fall of pressure to below 80 mm. illustrated in the lower curve of Fig. 1. The fact that cardio-acceleration slightly

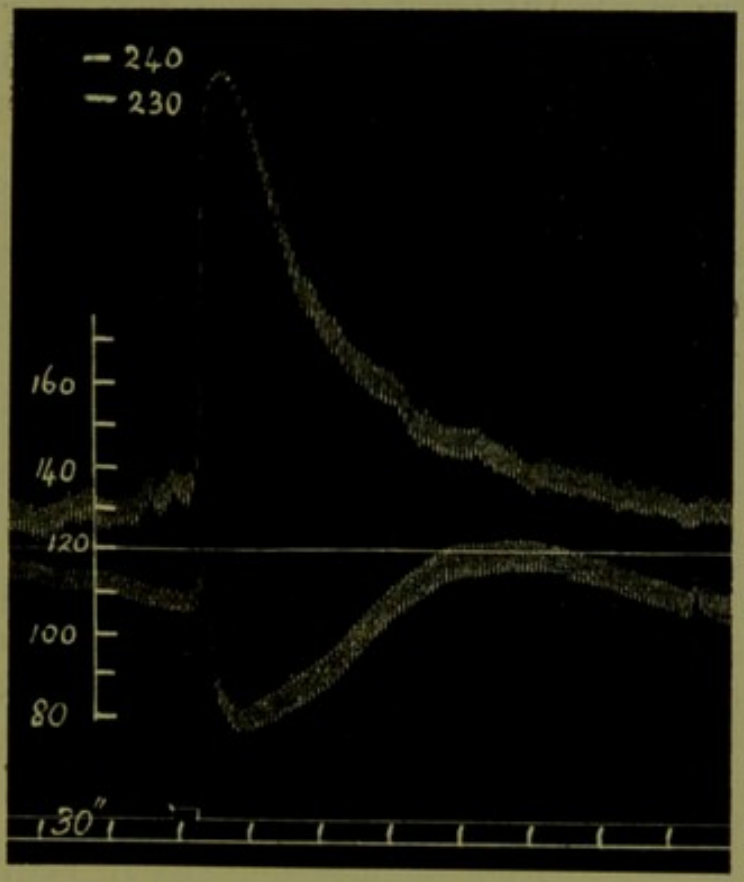

Fig. 1. Pithed cat: carotid blood-pressure. Upper curve shows effect of 0·025 mgm. of adrenine before, lower curve that of 0·1 mgm. of adrenine after 10 mgms. of ergotoxine.

anticipates the vasodilatation, and survives it for a considerable period, accounts for the small initial pressor peak, and for the long, low rise of pressure, which follows the marked fall. The line drawn at the 120 mm. level is common to the two curves, which have been mounted in vertical series for comparison. It is hardly necessary to emphasise the fact that a critical level of arterial tension, above which adrenine causes vasodilatation, and below which it causes vasoconstriction, will not account for the reversal here exhibited.

With smaller doses of ergotoxine, such as those used by Cannon and Lyman, the reversal of the adrenine effect is incomplete. Under

such conditions it can be observed that doses of adrenine which cause a fall of pressure, or a diphasic effect, while the pressure is still high as the result of the ergotoxine injection, cause a rise of pressure when the general level has again fallen; also that a small dose of adrenine may produce a fall, and a large dose immediately afterwards produce a rise. Even at such an early stage of ergotoxine poisoning, however, it will be found that a fall from high level is produced by doses of adrenine which always cause a rise in the normal animal, and that minute doses cause a fall from a level at which, before ergotoxine, they would have caused a rise. In other words, the effect of a small dose of ergotoxine is to lower the critical level of Cannon and Lyman. When a sufficient dose is given, as in the experiment quoted, the critical level approaches zero, in the sense that increasing the dose of adrenine merely increases the depth and persistence of the vasodilator effect, and that, however low the pressure falls, adrenine in any dose is incapable of producing vasoconstriction, though large doses may cause a small and prolonged rise of pressure from very low levels, owing to the incomplete extinction of the cardio-accelerator effect.

(2) *The vasodilator effect of splanchnic stimulation after ergotoxine.*

In an earlier paper I described the vasodilator fall of arterial pressure caused by stimulating the splanchnic nerves after adequate doses of ergotoxine. Since then, however, the experiments of Asher[1], Elliott[2] and others have shown that such stimulation accelerates the output of adrenine from the supra-renal glands. Elliott showed that this output of adrenine was responsible for the dip on the ascending limb of the blood-pressure curve caused by splanchnic stimulation in carnivora, and Cannon and Lyman have shown that splanchnic stimulation, in a cat with the abdominal viscera excluded from circulation, but the supra-renals intact, may cause a pure fall of blood-pressure, whereas, with the converse exclusion, they obtained only a rise, whatever the state of the arterial tension, and whatever the strength or rate of stimulus employed. This failure to obtain a fall of blood-pressure by splanchnic stimulation, with the supra-renal glands excluded, they regard as strong evidence against the presence of a vasodilator admixture in sympathetic nerves. It is clear that, if my interpretation of the vasodilator action of adrenine after ergotoxine, as indicating such an admixture, is correct, it is to be expected that stimulation of the

[1] *Zeitschr. f. Biol.* LVIII. p. 274. 1912.

[2] This *Journal*, XLIV. p. 374. 1912.

splanchnic nerves, after an adequate dose of ergotoxine, will cause a vasodilator fall of pressure, even when the supra-renal glands are extirpated. On the other hand, in accordance with the general experience, to which I have alluded elsewhere[1], that adrenine exaggerates inhibitor sympathetic effects as compared with motor effects, it is to be expected that the vasodilator effect will be relatively smaller, and more difficult to separate from the normally predominant vasoconstrictor effect, with splanchnic stimulation than with adrenine.

Exp. 2. (Cf. Fig. 2.) A cat was prepared as before and, in addition, the left supra-renal gland was removed completely, and the left splanchnic nerves isolated below the diaphragm, cut, and made ready for peripheral stimulation, the exposed viscera being protected by pads

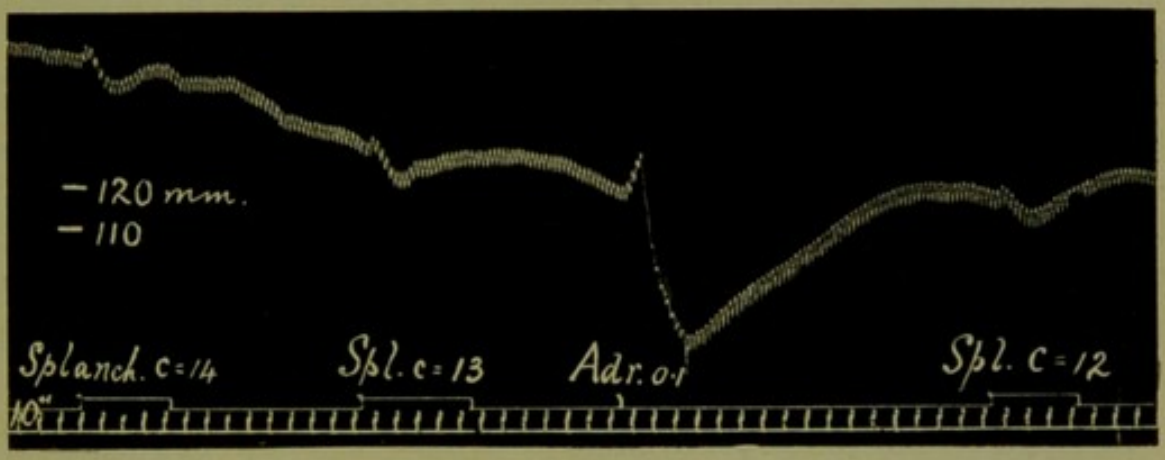

Fig. 2. Pithed cat: carotid blood-pressure. Left supra-renal extirpated. Effects of three stimulations of left splanchnic nerves, and of adrenine, after 10 mgms. of ergotoxine.

soaked in hot saline solution. An initial control stimulation caused a pure rise of blood-pressure. Two doses, each of 5 mgms. of ergotoxine phosphate, were then given intravenously. The result of three stimulations of the left splanchnic nerves, with increasing strength of stimulus, as the pressure fell after the second injection of ergotoxine, is shown in Fig. 2. An injection of 0·1 mgm. of adrenine is interposed, for comparison of the effect. It will be seen that each splanchnic stimulation causes a fall of blood-pressure, quite definite, but very small in comparison with that produced by a moderate dose of adrenine.

I have performed this experiment four times, and with uniform result. There can be no question of an effect on the contralateral supra-renal gland, as in two of the experiments both were extirpated. The effect can only be ascribed to a direct vasodilator effect of the

[1] This *Journal*, XLI. p. 54. 1910.

splanchnic nerves on the vessels of abdominal viscera[1]. The effect is, of course, comparable to the vasodilator action of the sympathetic nerves on the cat's foot after ergotoxine, which I recorded in 1906 (*loc. cit.* p. 175), though the observation did not lend itself to illustration. The fact that the similar effect of pure splanchnic stimulation, apart from supra-renal glands, has waited till now for its demonstration, is due to the fact that the participation of those glands in splanchnic effects has only recently been suspected.

(3) *The reversal of the effect of adrenine on the ferret's uterus.*

I have chosen this organ as suitable for experiment under the ideally simple conditions attained by isolation in a bath of warm, oxygenated Ringer's solution.

I showed in a previous section that adrenine lowers the blood-pressure after ergotoxine from a level lower than that from which, before ergotoxine, it produced a large simple rise. It might conceivably be objected, though I think in this instance not correctly, that the blood-pressure is not a safe index of arterial tension, since cardiac output, blood-volume, and the state of the venous reservoir are also involved.

In my earlier paper I showed[2] that the internal anal sphincter relaxed after ergotoxine in response to stimulation of the hypogastric nerves or injection of adrenine, though its tone was lower than when the same stimuli earlier produced contraction. It might be objected that a fall of tonus could be simulated by slight displacement of the recording balloon, though I do not believe that such occurred.

When an isolated horn of the uterus is fixed at one end to a rigid support and pulls by its other end on a lever, the problem of registration is reduced to its simplest form; when rise of the lever indicates increase in the tone of the plain muscle, fall of the lever must indicate diminution of tone. I knew from previous experiment that the uterus of the virgin ferret, like the bladder in the same species[3], gives a purely motor response to sympathetic stimulation, or to adrenine, which, in either case, is converted into an inhibitor response by ergotoxine.

[1] Dr Elliott informs me that he has also observed this fall of blood-pressure after ergotoxine, when the splanchnic nerves are stimulated after removal of the supra-renal glands.

[2] This *Journal*, xxxiv. p. 180. 1906.

[3] Elliott. This *Journal*, xxxv. p. 367. 1907.

The horn of the ferret's uterus, when isolated in warm oxygenated Ringer's solution, naturally assumes a low or moderate tonus, with a rhythm, which increases, as a rule, with the period of isolation from the body. The effects illustrated in Figs. 3 and 4, were obtained from a horn which had already been for some hours in Ringer's solution. The horizontal line across the tracings is continuous in the two

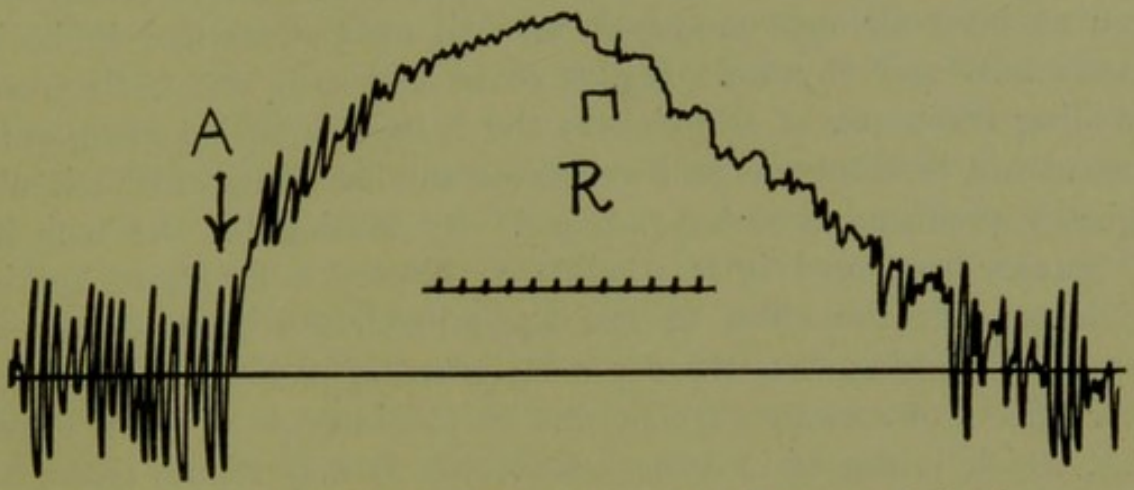

Fig. 3. Isolated uterus of virgin ferret. At *A* 0·1 mgm. of adrenine. At *R* fresh Ringer's solution.

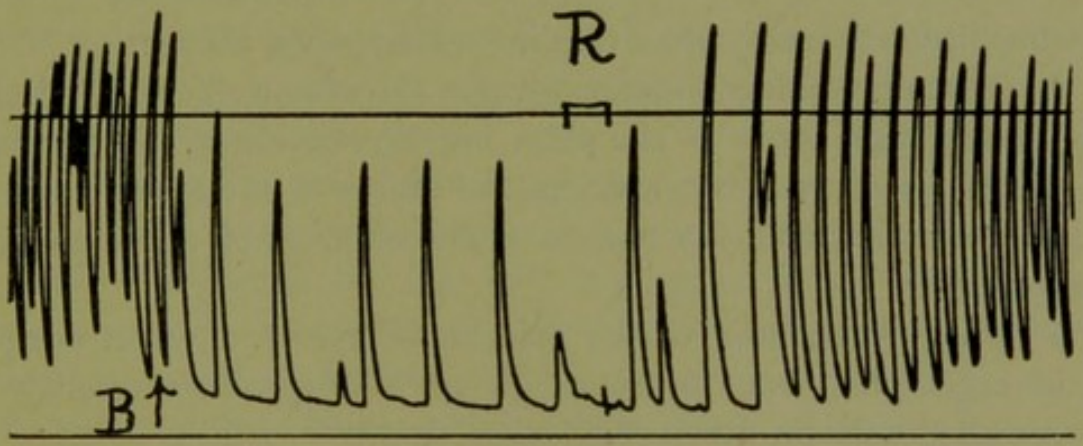

Fig. 4. Same as Fig. 3, after 2 mgms. Ergotoxine. At *B* 0·2 mgm. of adrenine. At *R* fresh Ringer's solution.

figures, and corresponds, therefore, to the same level of tonus in both. Fig. 3 shows the effect on the uterus, which has acquired a moderate tonus, of adding 0·1 mgm. of adrenine to the 250 c.c. of Ringer's solution in the bath. It will be seen that a pure rise of tonus, with partial obliteration of rhythm, results.

The adrenine was washed away with fresh Ringer's solution, and, when the tone had returned to the original level, 2 mgms. of ergotoxine phosphate, dissolved, with the aid of a little soda, in 2 c.c. of water,

were added to the bath. The result was a slow, but steady fall of tone to the minimum, the rhythm disappearing also. At this stage adrenine, even in large doses had no effect at all; the motor effect was paralysed, and inhibition impossible, since relaxation was already complete and rhythm absent. The ergotoxine was washed from the bath by several changes of Ringer's solution, and the tone then very slowly rose again, a somewhat exaggerated rhythm also appearing. Doses of adrenine given at intervals now produced, in each case, a marked inhibition of both tone and rhythm. Fig. 4 shows one such effect, the result of adding 0·2 mgm. of adrenine to the bath at a period when, as the figure shows, the tone was still well below the level from which adrenine originally produced a motor response. By waiting till the tone has still further recovered it is possible to display a far more striking inhibition; but the effect at the stage illustrated better serves my purpose of showing, that the reversing effect of ergotoxine on certain motor effects of adrenine is not due to the increase of plain muscle tonus, which it causes in some cases; that it may reduce tonus, and reverse the effect none the less.

Summary and discussion.

It has been shown by the experiments described above:

(1) That ergotoxine does not reverse the motor effects of adrenine by producing high tonus of the plain muscle concerned. Experiments on the blood-pressure of the cat and the uterus of the ferret show that it may lower tone and yet replace a motor effect of adrenine by an inhibitor effect.

(2) That stimulation of the splanchnic nerves, after an adequate dose of ergotoxine, may cause a fall of blood-pressure, though the supra-renal glands be removed.

My main concern is to remove any misconception which Cannon and Lyman's paper may have created as to the nature of the action of ergotoxine. With regard to the more theoretrical question, whether the fact, that certain sympathetic motor effects are reversed by this alkaloid, indicates the existence of a mixture of motor and inhibitor fibres in the sympathetic nerves concerned, I have little to add to what I wrote in 1906. Strictly speaking it is impossible to demonstrate the presence of either motor or inhibitor fibres to plain muscle in a mixed nerve in which the other predominates, unless they can be anatomically separated at some part of their course, as, for example, by stimulation of nerve-roots. The effect of any drug, or other influence, which brings

out an effect in the opposite direction to that usually observed, may always be attributed to altered response of the plain muscle. It is perfectly legitimate to maintain that ergotoxine acts by thus changing the direction of the response of certain tracts of plain muscle to sympathetic nerve impulses or to adrenine, provided that the unchanged effect of other kinds of stimulus is emphasised, and that the change is not attributed to the production of a permanent condition of tone. On the other hand the theory, that ergotoxine reveals a mixture by selective paralysis of motor myoneural junctions, still seems to me to explain more, in the sense that it enables us to summarise a larger number of the facts known as to its action. It accounts for the facts that, in many cases, where we have no reason to suspect an inhibitor admixture, ergotoxine causes merely a progressive and incomplete obliteration of a motor sympathetic effect; that where, on grounds of analogy from a related species, we have reason to suspect a masked inhibitor action, ergotoxine produces a typical reversal. It provides a meaning for the curious variations in motor and inhibitor activity of the series of amines closely related to adrenine, and the parallel variations in the ease with which their motor effects on certain organs, including the arteries, are reversed by ergotoxine[1]. The facts that the smallest doses of adrenine produce a rise of blood-pressure in the rabbit, however high the arterial tension, and that ergotoxine cannot reverse, but simply obliterates, the pressor action in this species, are intelligible on the view that the sympathetic supply to the arteries of this species, like that to its uterus, is of purely motor function, as contrasted with the mixed function in the dog and cat. And to me this seems an easier supposition, than to assume, as Cannon and Lyman must, that adrenine has an effect on the metabolism of arterial plain muscle in the rabbit, which differs fundamentally from that which it produces on arterial plain muscle in the cat and dog, but resembles its effect on other tracts of plain muscle in these carnivora. The effects of adrenine on extra-arterial plain muscle, whether of inhibition or augmentation, admittedly exhibit a close parallelism to those of the corresponding sympathetic nerves, and there seems but slender ground for assuming that the parallelism breaks down completely and singularly in the case of the vasomotor supply. There are, as I have mentioned already, numerous instances in which adrenine seems to produce inhibitor sympathetic effects with exaggerated prominence, but none other, so far as I am aware, in which it can be supposed to produce an inhibitor

[1] This *Journal*, XLI. pp. 45–51. 1910.

action which is entirely unrepresented in sympathetic innervation. I have weakened one of Cannon and Lyman's difficulties by showing that vasodilatation can be produced, after ergotoxine, by direct splanchnic stimulation. Their other chief objection—the "known organisation of the autonomic system"—can hardly be admitted as valid. Instances for a nerve supply of mixed function, from one source, are not wanting in this system, as, for example, the cranial autonomic innervation of the stomach through the vagus. Nor, apart from the cases which they rightly exclude as doubtful, are we without an independent example of vasodilators of true sympathetic origin; the sympathetic supply to the coronary arteries[1], the inhibitor effect of which is reproduced by adrenine[2], must, I imagine, be accepted as belonging to the true sympathetic system.

There is, indeed, no good evidence, apart from that furnished by the action of ergotoxine, for a mixed motor-inhibitor sympathetic supply to arteries in general; but, this being the possibility under discussion, its non-existence cannot be postulated as a feature of the "known organisation."

[1] Maass. *Pflüger's Arch.* LXXIV. p. 281. 1899.

[2] Langendorff. *Zentralb. f. Physiol.* XXI. p. 551. 1907. De Bonis and Susanna. *Ibid.* XXIII. p. 169. 1909.