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ON THE ENDOSMOTIC ACTION OF MEDICINES.

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THE celebrated attempt of M. Poiseuille to illustrate the mode of Action of Medicines by reference to the laws of Endosmose and Exosmose, in his memoir entitled "*Recherches Expérimentales sur les Médicaments*", in the *Comptes Rendus* of the French Academy of Sciences for 1844, led to the following inquiry; my intention being to take up the subject where he had left off, and to carry it further into detail. In repeating his experiments, however, as nearly as could be judged from the description, I perceived sources of fallacy attending some of the results, which quite destroy their value as examples of the phenomena to which they are compared. Even in the case of the saline purgatives, where the analogy appears to be the strongest, we may be allowed to question whether too much influence is not attributed to one agency of a purely physical nature, in producing effects on the living organism, which are more probably due to a combination of causes. On the other hand, some remarkable varieties of endosmose have come under my observation, coinciding with the peculiar properties according to which the substances concerned take their places in the classification of medicinal agents, and thus calculated, though on different grounds from those stated, to justify the opinion that endosmose really plays no unimportant part in the reactions which follow the presence of medicines in the system.

As a general result of the original investigations of Dutrochet, it may be stated, that when two miscible fluids of different density are separated from one another by a porous medium, two currents are established, one of greater intensity towards the denser fluid, and the other in the opposite direction. From the nature of the conditions under which they first attracted his notice, he was led to distinguish them by the names of Endosmose and Exosmose, signifying an impulse

inwardly and an impulse outwardly. He became convinced, however, that these terms had been unfortunately chosen, by such proofs as the following. If a piece of intestine, closed at both ends and filled with a solution of gum, be immersed in water, it becomes distended by the stronger current inwards, here properly called that of endosmose. But if the relative position of the fluids be reversed, the solution of gum being exterior, the stronger current is then directed outwards, and the weaker towards the interior of the cavity. Dutrochet expresses his regret for the too hasty adoption of terms which are thus calculated to convey a wrong impression; but, as they had got into general use, he prefers allowing them to remain, with the understanding that endosmose refers solely to the stronger, and exosmose to the weaker current. According to Poiseuille, when a fluid is taken into the stomach, it comes in contact with the epithelium of the mucous membrane; and penetrating this, it enters into relation with the capillaries of the villousities. A double current ensues; part of the serum passes through the walls of the vessels and mingles with the foreign fluid, while some of the latter enters the blood, and is carried into the circulation. If the mutual interchange is equal, no alteration occurs in the bulk of the fluid on either side; but if there be an endosmose of the serum towards the bowels, an accumulation takes place in the latter; they contract, to get rid of their contents, and the foreign fluid thus acts as a *purgative*. The opposite effect is said to be produced when the stronger current proceeds from the bowels towards the blood-vessels. There are stated to be few exceptions to this rule; and when they occur, it is either because the foreign substance penetrating the membrane renders it unsuitable for endosmose—in other words, makes it permeable, like a filter, to whichever of the fluids exerts the greater pressure; or because the substance puts a stop to the action altogether, the membrane becoming impervious to either fluid.

The endosmometer employed by Poiseuille may be presumed to have been similar to that of Dutrochet, which has some inconveniences worthy of notice. For the membrane he used the cæcum of the sheep, but whether fresh or in what state is not mentioned. Having closed the reservoir with a piece of the cæcum, and filled it with the fluid to be tried, he immersed it in serum. But though the mode of preparing the fluid in the reservoir is commonly stated, yet whence its density may be ascertained, the density of the serum, and the animal which furnished it, are not stated. That of the human (venous) blood, according to Becquerel and Rodier, varies from 1026 to 1030, while the numbers given by Dr. John Davy for the venous blood of some of the lower mammalia, are from 1023 to 1030. The last, or one or two degrees higher, was what I obtained for the mixed serum of the sheep killed for the table. This question of the density of the serum is a matter of some consequence; for though, where the difference between the fluids in this respect is known to be considerable, a doubt as to a few degrees on either side may not seriously affect the conclusion, the case is altered when, for instance, a theory of the influence of tobacco is founded on an experiment in which the specific gravity of a decoction may be somewhere between 1020 and 1030, and that of the serum opposed to it is also uncertain.

The endosmometer of Dutrochet consists of a glass tube with a

somewhat bell-shaped moveable expansion, called the reservoir, open at both ends. The tube is fitted into a neck at the smaller end by the aid of a cork. A piece of membrane having been tied over the larger orifice, the instrument is filled and placed in another vessel of fluid, the pressure of which causes that in the reservoir to mount to a certain height in the tube. This is noted by the aid of a scale attached to the tube, and affords the starting point for future observations. Apparently to allow the membrane to be secured, there is a deep contraction round the middle of the reservoir, which has the disadvantage of requiring a needless expenditure of material. The use of corks for fitting the tubes also rendered it difficult in my experiments to prevent loss from leakage. Accordingly, the form I have adopted is that of a bell jar, having a projecting rim round the larger opening, by which to fasten the membrane, and the cork in the neck is also dispensed with, by having the end of the tube and the inside of the neck ground to fit one another. To sustain the instrument in the required position, the tube is passed through a cork adapted to a hole in a leaden plate, which rests on the edge of the outer vessel. This is a glass cylinder of such dimensions that, when containing a quantity of fluid equal to that in the reservoir, a portion is raised by the introduction of the reservoir to a level with its neck, leaving sufficient below the membrane. The height of the column in the tube is then marked by a thread, and the subsequent changes being noted by the same means, are measured by a pair of compasses on a scale of inches and tenths. The reservoir has a capacity of eighteen drachms, and a diameter at the larger orifice of 1·8 inch. The calibre of the tube is a fourteenth of an inch. Smaller instruments were used for the skins of frogs, etc.

Dutrochet and Matteucci recommend to support the membrane by resting it on a perforated metallic plate. But if it be firmly stretched, to which no objection has been stated, it seems to afford sufficient resistance to pressure; and, besides, a question arises, as to whether the presence of the metal does not tend to disturb the results. It was observed by M. Porrett, that when two portions of distilled water are separated by a membrane, and connected each with a pole of a galvanic battery, the water traverses the partition towards the negative pole. This resembles the effect of difference of density, and suggested the theory of Dutrochet, that some electrical influence is the cause of endosmose and exosmose. Nevertheless he tried in vain to determine the point by the aid of the galvanometer. On filling a reservoir with a solution and suspending it in water, I have also found no effect produced on the needle on connecting the opposite sides of the membrane with a galvanometer; but the addition of a plate of tinned iron in the position indicated, gave rise to deflections varying in extent with the nature of the fluid employed.

But the question of most consequence is that relating to the condition of the membrane, a distinct account of which, as will presently appear, is by no means a matter of such indifference as might be supposed, from the loose manner in which it is commonly mentioned by authors. This is sufficiently shown by the researches of Matteucci, although it is doubtful whether his theoretical inferences are not somewhat premature. In trying the skins of the frog, eel, and torpedo, he found a remarkable difference of result, according to the position of

the respective surfaces with regard to the fluids, the endosmose being greater when the outside was in contact with the denser fluid. Or, supposing the rule to hold good in the live animal, the tendency of the skin to allow fluids to pass outwards exceeds its disposition to absorb them. In the author's words—"If we do not admit that this secretion of mucus, and this weak absorption of the water in which these animals live, (functions which for their normal performance ought always to be in a certain relation to each other), are entirely due to this phenomenon, it is undeniable that they must be promoted by it." (*Lectures*, translated by Pereira.)

With syrup of the high density employed by Matteucci, opposed to water, the same result is readily obtained, as regards the skin of the frog. There is one remarkable source of fallacy, however, to be disposed of before we proceed to reason physiologically on the subject. After the experiment has lasted several hours, the cuticle, where it is exterior on the reservoir, can be easily taken off, and then the endosmose increases rapidly, so as greatly to exceed what could otherwise be obtained in either position of the surfaces. Eel skins, under my observation, gave variable results; even when perfectly fresh, (as the author enjoins), an unequal flow of mucus took place from the naturally free surface, which was a constant source of perplexity. The skin of the torpedo I have had no opportunity of examining. Matteucci's researches were extended to the mucous membrane of the stomach and bladder of different animals, with the effect of showing that the intensity and direction of the endosmotic current vary with the nature of the membrane, and that "the cases are very rare in which, with fresh membrane, endosmose takes place equally, whatever be the relative position of the membrane to the two liquids." But the mucous lining need not be insulated to observe a difference of result according to the position of the surfaces, for on using portions of the fresh cæcum of the sheep, with the inside in contact with strong syrup, the effect I found was much greater than in the reverse position. When the density of the syrup, however, did not exceed 1060, (which was the usual standard in my experiments), it was too obscure in either case to admit of a satisfactory comparison.

Conceiving from the last circumstance that Poiseuille was not likely to have used the cæcum in the fresh state, I tried it after having been first dried and then thoroughly moistened. The effect was more decided, but still, on the whole, the phenomena did not agree with those described. On further reflection, I was led to try this portion of the intestine as sold by the French in a prepared state, when it consists of the peritoneal coat separated from the other tissues. In comparison with such other dried membranes as appear most likely to answer, it has hitherto appeared to deserve the preference from the greater delicacy, though not otherwise dissimilar character, of the indications afforded by it. Among those employed were the cuticle lining the gullet of the ox (the "weasand" of commerce), and the prepared intestine of the sheep, as used by the druggists, both seemingly well suited for the purpose. An idea of their comparative value may be formed from the following table, which shows the effect with different solutions opposed to distilled water for the space of five hours. At the same time an illustration is afforded of a law, to be more par-

ticularly noticed hereafter, that the amount of endosmose varies with the nature of the fluid, and does not depend entirely on the density.

DENSITY OF SOLUTIONS 1060.

PREPARED CÆCUM.					DRUGGISTS' MEMBRANE.				
Elevation in inches.	Syrup.	Salt.	Sulph. Mag.	Nitra.	Elevation in inches.	Syrup.	Salt.	Sulph. Mag.	Nitre.
1st hour	2·3	2·1	1·	·7	1st hour	1·1	·6	·4	·1
2nd —	2·2	1·2	1·	·3	2nd —	1·1	·4	·4	—
3rd —	2·1	·5	1·	—	3rd —	·8	·2	·4	—
4th —	1·5	·1	1·	—	4th —	·7	—	·2	—
5th —	1·	—	·9	—	5th —	·5	—	·2	—
DRIED CÆCUM.					"WEASAND."				
1st —	·7	·5	·1	descent ·4	1st —	·3	·2	·1	—
2nd —	·5	·3	·2	—	2nd —	·3	·2	·1	·1
3rd —	·4	·2	·2	—	3rd —	·2	·2	·1	—
4th —	·3	·2	·2	—	4th —	·2	·2	·1	—
5th —	·2	—	·2	—	5th —	·2	·1	·1	—

Returning now to consider the views of Poiseuille, I shall confine myself to such as are deduced from experiment, following the order observed in his memoir.

ACTION OF PURGATIVES. Seidlitz water contained in the reservoir being opposed to serum ascended in the tube, albumen was found in the reservoir, and sulphate of magnesia (a constituent of Seidlitz water) in the serum. Patients having been purged with Seidlitz water, the alvine discharges contained an unusual quantity of albumen, and the urine of sulphate of magnesia. Pullna water gave the same results. Strong solutions of various salts and extracts likewise produced endosmose of the serum. Hence the conclusion is, that the influence of purgatives, relatively to the alvine discharges, depends on their property of determining a flow of serum into the bowels; while it is admitted at the same time, that all substances which have this property are not purgatives, neither do all purgatives act by producing endosmose. Syrup, for example, is a powerful endosmotic agent, but it is decomposed by the gastric juice before reaching the intestines; and, again, some purgatives, such as gamboge, operate by exciting the peristaltic action of the intestines. As regards the value of the experiment, notwithstanding its importance as showing that endosmose may probably have some effect in the manner indicated, we may reasonably question whether serum be a fair representative of the living fluid in the blood-vessels, or its accumulation in the bowels the only physiological effect of the saline purgatives.

TOLERANCE OF MEDICINES. It is proper to premise what is said on this subject, with a statement of some phenomena to be commonly observed in experiments on endosmose. The process, having been established, stops at periods varying with the substances employed. If the outer fluid be then examined, it appears striated, from the incomplete diffusion of the foreign matter introduced into it. After shaking it, there is a renewed ascent of the column; and the same thing may happen repeatedly. Poiseuille's experiment to illustrate the tolerance of medicines, is as follows: A solution of phosphate of

soda contained in the reservoir being opposed to serum, the column rose in the tube. On ceasing, the effect was renewed by agitation; and again it recurred on the substitution of water for the serum. It was further reproduced by removing the water, and replacing the serum previously withdrawn. And, finally, a fresh substitution of water for the serum produced it for the fifth time. The first pause the author attributes to a change in the condition of the membrane, rendering it unsuitable for endosmose; though he observes in the next sentence, that the agitation caused the displacement of the strata of fluid in contact with the membrane, which permitted the action to go on. On repeating the experiment with a solution of the phosphate, of density 1060, and the serum of the sheep, I obtained similar alternations, except that the second employment of the serum was not followed by a repetition of the phenomenon. Whether the author's facts, as related, bear the application he makes of them, I shall not further undertake to decide. "We believe," he says, "that the same substance taken into the stomach, and passing through a greater or less portion of the intestines, will produce less striking effects, as it is more frequently employed; hence we are led to infer that the tolerance in diseases invoked by Rasori, Giacomini, and the other Italian physicians, depends simply on the circumstance that the membranes of the canal in continued contact with the same substance, become saturated, and unable to allow it to enter so freely into the circulation."

INFLUENCE OF OPIUM. It is observed that opium and its salts check diarrhœa, and prevent other medicines, when given for special objects, such as nitre for rheumatism, from operating as purgatives. A solution of a drachm of nitrate of potash, to an ounce of water, was opposed to serum. It produced an elevation of the column for three quarters of an hour. While the operation was proceeding "in all its intensity", the instrument was withdrawn, and its contents replaced with a similar solution containing muriate of morphia. After this the action continued, but less vigorously; the column ascended for an hour, rested an hour, and then began to descend. Thus it is said the morphia diminished the endosmose, then stopped it, and ended by producing exosmose; such being precisely its effect in promoting constipation of the bowels.

After a careful investigation, I am compelled to say that my results are opposed to this doctrine.

In the first place, if the experiment had been continued without the morphia, the probability is, that the action would have ceased about the same time; because, as shown by the above table, nitre itself appears to have but a comparatively feeble power of endosmose. Solutions of the same strength, when opposed to the serum of the sheep, produced only an elevation of half an inch, and stopped within an hour. As no other evidence is adduced in support of the theory, it might fairly be regarded as unsatisfactory. But to determine whether opium, under any circumstances, exerts this peculiar influence on the membrane, I have repeatedly tried it in aqueous solution opposed to water, and obtained elevations far more considerable and lasting than those afforded by many inorganic salts. The serum of the sheep, enclosed in the reservoir, being opposed to a solution of a grain of muriate of morphia to an ounce of distilled water, occasioned a vigor-

ous endosmotic action for above twenty-four hours. Added to syrup or a solution of sulphate of magnesia, of density 1060, in the same proportion, or dissolved in the distilled water opposed to them, it made no appreciable difference. Hence there is reason to doubt whether morphia is "a substance the presence of which puts a stop to endosmose, and renders the membrane impermeable to either fluid."

INFLUENCE OF TOBACCO. The decoction of tobacco is stated by Poiseuille to have the effect of penetrating the membrane and rendering it permeable, so as to be unsuitable for endosmose. He made a decoction of four parts of tobacco-leaves to forty of distilled water, and opposed it to serum. In his own words, "there was a depression of the liquid column in the tube of the endosmometer; *the same effect is produced* on inverting the order of the two liquids, that is, putting the serum into the reservoir, and the decoction outside."

However, no allusion is made to the specific gravities. Having made a decoction in the same proportions, I found the density, after boiling above an hour, was 1023; and this, as expected, did not produce endosmose with the serum of the sheep. But a portion of the same decoction being opposed to distilled water, caused the column to ascend for more than five hours, at the rate first of three, and then of two-tenths of an inch per hour. After having been used for this purpose, the membrane appeared to be quite efficient when exposed to the action of syrup. No deteriorating effect seemed to follow from mixing a drop of nicotine with distilled water external to a reservoir filled with syrup. But what, I think, settles the question most completely, is that a decoction of tobacco, boiled down to a density of 1052, being opposed to the serum of the sheep at 1031, the endosmose was very active, averaging .7 inch consecutively during the first five hours, and was found not to have ceased in twenty-one hours from the commencement. A watery solution of the extract of hyoscyamus (which belongs to the same natural family as tobacco), also produced endosmose, with no perceptible deterioration of the membrane.

Having observed, as above noticed, a decided want of uniformity in the amount of endosmose afforded by different solutions, of equal density, under the same conditions, I was induced to extend the investigation to classes of substances. A large number were therefore submitted to experiment, the reservoir being closed with the prepared cæcum, previously soaked about three hours in cold water, filled with the solution at 1060 (or saturated, when the substance was not soluble, to that extent), and plunged in distilled water, equal in quantity to the fluid in the reservoir. The elevations were noted at intervals of an hour. Two instruments were employed for each substance simultaneously; and the operation was then repeated with fresh materials, to furnish a mean result, which was set down in a table. The limit of five hours was chosen for the experiment; first, because the action generally ceased within that period, so that it formed a tolerable standard of the extreme duration of the endosmose; and next, in order to learn whether the observed deficiencies in this respect were attributable or not to an obstruction of the pores of the membrane. This appeared not to be the case, from the circumstance of the water being usually most densely impregnated where the action had been

the smallest, as measured by the elevation in the tube. It is necessary to mention that the apparatus was never shaken, as this would tend to confuse the results.

The table itself I shall refrain at present from laying before the public, because, notwithstanding the care taken in its construction, it may still be calculated to mislead, from the difficulty of ascertaining the precise relation between any two substances. Dutrochet, in comparing gelatine and albumen relatively to the amount of endosmose which takes place between them and water, was not satisfied with less than ten experiments. The acquisition of a suitable porous medium is, in fact, a great desideratum, it being impossible as yet to depend on the uniformity of structure, even of adjoining portions of the most carefully selected membrane. I shall therefore content myself with mentioning the substances examined, and stating the general conclusions, without prematurely attempting to define the exact relation in which they stand to one another.

Sulphates. Potash, soda, ammonia, magnesia, alumina and potash, iron, copper, zinc.

Nitrates. Potash, soda, ammonia, lime, baryta, strontia, lead, copper.

Chlorate. Potash.

Phosphate. Soda.

Biborate. Soda.

Carbonates. Potash, soda. *Sesquicarbonate.* Ammonia. *Bicarbonates.* Potash, soda.

Tartrates. Potash, Potash and soda.

Acetates. Potash, soda, ammonia, lead.

Chlorides. Potassium, sodium, ammonium, calcium, magnesium, barium.

Iodide, Bromide, Ferrocyanide. Potassium.

Organic Substances. Gum, liquorice, sugar, treacle, opium, tobacco, hyoscyamus, spirit of turpentine.

Among the salts enumerated, the sulphates, the phosphate and biborate of soda, the carbonates, tartrates, and acetates, all displayed a great degree of energy, though the action was of a different character. In the sulphates, it was less vigorous in the early stages; but it maintained itself more equably, and was generally unfinished at the close of the experiment. The others, except the borax, gave much higher results at first, but the rate of elevation per hour diminished rapidly. On the other hand, the nitrates, the chlorate of potash, the chlorides and their allied salts, were remarkable for their generally feeble action, especially the chlorate of potash, and the iodide and bromide of potassium. Among these, the chloride of sodium was distinguished for its comparative degree of energy, and the length of time it was sustained. Now, what deserves attention here, relatively to the medicinal employment of these substances, is, that those which are preferred as purgatives belong to the more energetic class of endosmotic agents; and again, that experience has fixed upon two of the *sulphates* as the best adapted for ordinary use. Between the endosmose of the sulphate of magnesia, and that of the nitrate of potash, equally familiar as a diuretic, there was always a striking contrast, to the advantage of the former. Some of the same endosmotic class as the last salt, but of a still feebler character, as above specified, have at the same time an

obscure and undefined action when given medicinally, characterised as resolvent, discutient, etc. The elevation of gum and liquorice is slow, but of extraordinary durability, lasting for days, and even weeks, without interruption. These are the common demulcents.

But there are other salts in the list, which exhibit similar properties in the endosmometer to those of the medicinal agents just noticed, and nevertheless are prescribed for very different purposes. This might be supposed to prove that the force in question has, in reality, very little influence. I am not attempting to establish a theory by which all the varieties in the action of medicines may be accounted for by modifications of endosmose; and, indeed, as already stated, I imagine it to be but one among a combination of agencies which regulate their effects. In consequence, the word "coincidences" appears to me preferable to express the relations just pointed out. At the same time, I cannot help thinking that these are too remarkable not to be considered as of some importance, and worthy of leading to further investigation. It is beyond doubt that processes of endosmose and exosmose are constantly going on in the system, and reason would suggest that they must be qualified by the inherent tendencies, in this respect, of the various bodies in solution. The above apparently exceptional cases, it will be observed, are those in which there is usually some peculiar irritant or poisonous property, which takes the pre-eminence as regards the sensible effects, but does not necessarily exclude the operation of this agency. It may be added, that another striking coincidence is presented by alcohol and ether, which, as ascertained by Dutrochet, though lighter than water, act towards it like fluids of greater density, and attract it through the membrane. I have found that spirit of turpentine has the same effect, though only to a slight extent, probably from its being but sparingly soluble in water. This appears curiously significant, when associated with the peculiar intoxicating properties of these fluids.

It may be remarked, that Dutrochet was aware of a diversity in the endosmose of different substances, irrespectively of the relation of density; and suggests in his collected memoirs, published in 1837, that "it would be important to determine by experiment the relative power possessed by different solutions, when separated from water by the same animal membrane." He tried the experiment himself, in the case of gelatine, albumen, gum and sugar, and two of the inorganic salts. The proportion of the endosmose of gum to that of sugar was as eight to seventeen, which agrees very nearly with my results. The salts were sulphate of soda and chloride of sodium, which gave the proportion of two to one; while the numbers I have marked in the table are, for sulphate of soda 6·6 inches, and for chloride of sodium 3·9 inches elevation in five hours. This is a sufficiently close correspondence to show that Dutrochet's researches, had they been carried further, would probably have led to the same results as those which are here given.

From what precedes, I think the following conclusions may be drawn:

1. That the division of substances into those which are favourable to endosmose, and those which, on the one hand, retard and annihilate it by their influence on the membrane, and on the other, render the

membrane permeable, or reduce it to the condition of a filter, is without sufficient foundation.

2. That the power of endosmose of different substances is not regulated entirely by their density, as already observed by Dutrochet.

3. That the purgative salts generally have an energetic power of endosmose, and that this is exerted with more steadiness and uniformity by those which medical experience has selected as the most useful in ordinary cases.

4. That some of the other substances examined have marked peculiarities with regard to endosmose, which will probably assist towards explaining their mode of action on the system.

London, December 1851.

THE LIVER THE REGENERATOR OR HYDROGENATOR IN ANIMALS; OR THE ANTAGONISM BETWEEN THE LUNGS AND THE LIVER.

By GEORGE WYLD, M.D.

THE object of this paper is to disprove the doctrine, so universally prevalent, of the liver being mainly an organ for the excretion of the waste of the tissues, and thus *vicarious* with the lungs; and to propound the idea of the writer, that the liver is essentially a *secreting* organ in *antagonism* with the lungs. Or, that, as the lungs are mainly for the *oxydation* of the system and destruction of the tissues, so the liver is mainly for the *hydrogenation* of the system and regeneration of the tissues.

The following (abbreviated) quotations will fully exhibit the prevalent doctrine concerning the function of the liver to be as above stated.

Müller says the liver *frees the blood* from an excess of matters containing carbon and hydrogen, as the kidneys remove the superabundance of those materials, which contain a large proportion of nitrogen. (pp. 164, 165.)

Tiedemann and Gmelin say that the excess of bile secreted in the tropics is required to compensate for the diminished purification of the blood in the lungs, on account of the rarification of the air. (Müller, p. 166.)

Carpenter, in his *Physiology*, 1842, says: "The rudimentary structure of the liver in insects is compensated for by the extremely active respiration of these beings, while in molluscs the liver attains a greater development; and we are at once struck with the fact that the liver bears an inverse proportion to the opportunity afforded by the respiratory organs for the aëration of the blood. In fishes and reptiles the liver is of considerable size, and seems to perform a very important part in the decarbonisation of the blood. In birds, on the other hand, where respiration is so much more active, the liver is smaller." (pp. 439, 440.)