Many other instances could be cited of remarkable developments in industrial processes, if the time permitted.

In the early ages of civilization, slavery was probably essential to progress because only through the enforced labor of the many could the few find time to think. The first use of mechanical power freed the slaves of the Roman Empire from their most arduous labor; but its service to mankind was very slight up to the beginning of the eighteenth century, when a skilled workman could earn in a week only the equivalent of two to three bushels of wheat. Mechanical power then relieved animal power in pumping water from mines and brought coal in large quantities to the service of mankind.

The great inventions in spinning and weaving in the latter part of the eighteenth century, and the application to other purposes of the same fundamental principle, namely, that of transferring the workman's skill and intelligence to machinery, multiplied the uses of mechanical power; but the development was comparatively slow up to about 1870. Just before this date, many of the state universities and endowed technical schools had been founded. The supply of scientifically trained men graduated therefrom resulted in an accelerated development of the production of mechanical power and its utilization by machinery for almost every purpose, thereby causing such widely diffused material prosperity that the skilled worker's weekly wages are now equivalent to twenty to thirty bushels of wheat.

In the fifty years from 1869 to 1919, the population of the United States increased 2.76 times. In spite of the shift in population from the country to the city, so that only one quarter of those in gainful occupations were employed in agriculture in 1919, while nearly one half were so engaged in 1869, the agricultural production increased 4.94 times, or 80 per cent. more rapidly than the population. During the same fifty years, the products of mines increased 18.81 times or nearly seven times more rapidly than the population. The manufactured products increased 9.61 times, or about 3.5 times more rapidly than the population. While many factors contributed to these increased outputs, the most important factor is undoubtedly the increased production and utilization of mechanical power by machinery.

To-day, the drudgery of the struggle for existence has largely been transferred to machinery vitalized by mechanical power, thus making universal education possible by sparing youth from the farm and the factory. May we be able to maintain and even improve our material prosperity by developing more economical methods of producing and utilizing mechanical power—for our necessities of existence must be met before we can find leisure for intellectual development.

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ON THE BASIS FOR THE PHYSIOLOGICAL ACTIVITY OF CERTAIN ONIUM COMPOUNDS[1]

I. INTRODUCTORY PAPER[2]

THE problem of determining the basis for the physiological activity of any substance presents almost insuperable difficulties in the present state of our knowledge of the physics and chemistry of the living cell. In fact, there are those who feel that the problem is not solvable at all, until definite knowledge of living processes is available.

While it is true that a very great amount of work has been done in attempts to determine relationships existing between physiological activity and chemical structure and a number of interesting generalizations within restricted fields have been made, still from all this work substantially nothing has come to light concerning the actual mechanism of the action of any particular substance in the cell. The same may be said of the results that have been obtained in attempting to correlate physiological activity with physical properties.

The difficulties involved are many sided. Some of the first obstacles encountered have to do with limitations of theory and methods of fundamental sciences. The methods of determining, particularly in a biological environment, the various physical effects, as osmotic pressure, distribution, adsorption, interfacial tension, electrical, etc., are deplorably inadequate.[3]

Much, in fact most, of the work done in attempts to deduce correlations with physiological activity has been carried on with substances of rather intricate structures by changing groups involving only a small fraction of the mass of the complex molecule. The effect of this alteration of "side chains" on stability, tautomerism, physical properties, etc., might have been either overlooked or difficult to evaluate. Then, too,

[1] This problem is being carried on in cooperation with Dr. Reid Hunt, of the Harvard Medical School. The physiological data is the basis of another series of papers published elsewhere by him.

[2] Adapted from a lecture given before the New York Section of the American Chemical Society, June 6, 1924.

[3] One can hardly refrain from expressing regret that so few of the better minds in physical chemistry and physics have become interested in the biological applications of their fields.

it would appear that very often the type of physiological activity selected for study has not been that which could be of value from the point of view of mechanism. This is well illustrated in the work on narcotics. General narcosis is entirely too gross an action to be of value in the study of relationship with structure or even physical properties excepting only when members of a homologous series are compared. To appreciate this fully one needs to know hardly more about that subject than that narcotic action can be brought about with nearly equal facility by substance differing in chemical structure and physical properties, as do magnesium chloride, chloroform, benzyl alcohol, sulfonal and cocaine. These substances have altogether too many points of dissimilarity.

Notwithstanding the great difficulties that must be overcome in the solution of this problem and irrespective of the certainty that much of the work on it would yield results of negative value only, it still seems abundantly worth while. The urge for a carefully planned systematic study is of course evident. Until something definite is known concerning the mechanism of the action of drugs, there will be available neither a rational basis for the treatment of a large class of diseases, nor will there be a foundation from which one can systematically develop new curative agents. Without a knowledge, too, of how neurotic drugs act, there can be no true picture drawn of the action of the hormones which delicately balance the processes of normal life.

Evidently in a problem in which there is so much of the intangible, in which the difficulties are enhanced so largely by faulty methods and imperfect theory and in which there must necessarily be combined intimate knowledge of different sciences, it is especially desirable that the point of attack be carefully considered. Probably the problem will only be solved by the combined and coordinated efforts of experts in several sciences.

It would seem that attention should be given first of all to the physiological response to be investigated. This should be as definite as possible and not be given by varied classes of compounds. The substances, too, which are to be investigated should be as specific in their action as possible, that is, within definite concentration limits they should approach as nearly as can be the ideal of acting on only one type of tissue giving a single physiological response so that there will be little ambiguity as to the seat of their action. In addition their structure should be as simple as possible.

Upon considering the foregoing, we have chosen the onium compounds of the choline type. These compounds have to an unusual degree a high product of specificity of action with simplicity of structure. The choice of this class of substance is desirable, too, because through the brilliant work of Reid Hunt[4] in America and Dale[5] in England, methods have been developed for estimating the relative action of these on different nerve tissues and a great deal of pharmacological data has been made available, particularly by Hunt.

Structurally the substances are quite simple. They are alkyl and substituted alkyl onium compounds. It has been found possible by varying the substituent in one of these alkyl groups to change the physiological activity by several thousand per cent. The most striking examples of this is the effect of acetylation of choline discovered by Hunt.

Substances of this type exhibit in general three types[6] of physiological activity. They show in a quite varying degree the curare action of paralysis of the motor nerves. This action seems to be a stoppage of the nerve impulse by the action of the substance on a mechanism which couples nerve endings with the muscle (myoneural junction). While in many ways this action is of much interest, on the whole it is produced by too wide a variety of materials to be sufficiently characteristic.

A second action is the muscarine effect which is produced by the substance when present in a definite concentration range. The most readily measured result of this is a lowering of the blood pressure. The heart is slowed by stimulating the ends of the parasympathetic nerves to this organ and this, with an analogous action on the blood vessels, causes the lowering of the blood pressure.

The third physiological response is a nicotine-like action produced by these substances in relatively higher concentrations. This is made evident by a rise of arterial pressure due to a stimulation of the nerve cells of the autonomic ganglia. The action is on the cell of the peripheral neuron.

Since these actions can be studied independently[7] and since in each case the action is on a very definite structural element of the nervous system they should lend themselves with exceptional facility to the study

[4] Reid Hunt, *Am. Journ. Physiol., 45,* 231 (1918), and earlier papers therein cited.

[5] Dale, *Journ. Pharm. and Exper. Therap., 6,* 147 (1914), and earlier papers.

[6] There are two other physiological effects which may be produced by these substances. These are, however, less well defined. They may or may not produce muscular tremors and paralysis of the ganglion cells of the autonomic system.

[7] For methods of study, see papers by Hunt (Ref. No. 4) and by Dale (Ref. No. 5).

of the mechanism of drug action. We have prepared a number of ions of the general formulas R_4M^+ and $R_3M-R'-A^+$ where the Rs are alkyl and aryl-alkyl groups and where A is any substituent as $-OH$, $-SH$, $-NO_2$, various esters, etc. M represents elements of the nitrogen and oxygen families. With the latter only three radicals will be joined to the onium element. Selected members of these series are being studied from the points of view of their stability, and their electrical, surface tension, adsorption, etc., effects as well as in certain cases their X-ray spectra and special configuration. The various stimulating and paralytic effects on the nerve impulse have been compared by Dr. Reid Hunt.

Almost every chemical and physical property has at some time been suggested as the basis for the action of drugs on the nervous system. For the most part these speculations have been considered specifically with reference to narcotics. As applied to the action of the compounds here considered all of them are distinctly inadequate.

While this appears not to be the place to consider critically all these theories, the following observations may be made with reference to the bearing that the results we have obtained have on certain of them.

Both H. Meyer[8] and H. Fühner[9] have advanced the idea that the curare action of the quaternary compounds of nitrogen, phosphorus, arsenic, antimony and sulfur depends upon the basicity of the corresponding bases. A comparison of the earlier pharmacological data with the results of conductivity determination made by Bredig[10] on a number of the tri and tetra alkylated derivatives of these elements seemed to give some basis for this statement. Hill,[11] however, has shown that in at least one case (tetramethyl ammonium hydroxide) Bredig's results are in error, and a careful investigation by Hunt[12] of a number of our products has brought out several interesting irregularities in their physiological activity. It was found that the tetra methyl derivatives of arsenic and antimony as opposed to those of nitrogen, phosphorus and sulfur did not give the paralytic curare effect nor the stimulating nicotine effect but did give like derivatives of those elements, the stimulating muscarine action (stimulation of the parasympathetic nerve endings to the heart and of certain other organs and a dilation of blood vessels). The less alkylated derivatives of these two elements are without basic properties, but the quaternary compounds approach those of nitrogen in basicity and according to this theory should approach those of nitrogen in stopping the electrical impulse from the nerve ending to the muscle. While these and also other facts throw out the idea that their strength as bases is a factor in determining the physiological activity of these substances, still one is forced to the belief that some sort of an electrical property is involved.

All substances giving the stimulating nicotine and muscarine actions and many giving the paralytic curare effect are cations. We have recently obtained very interesting proof of the importance of the character of the electrical charge on these ions in the study of certain "betaine esters" (carbethoxy methyltrimethyl ammonium salts and homologues and analogues). Betaine is physiologically inert because, we believe, it exists in the blood substantially wholly as the electrically inert inner salt (bipolar ion, $[(CH_3)_3N-CH_2\,COO]^{\pm}$). It has been found that when this carboxyl group is esterified and the onium grouping becomes a cation, the striking physiological activity of choline is manifest.

The desirability of a very precise study of the electrical properties of certain of these physiologically active ions seems evident. Such an investigation is being carried on in this laboratory and a preliminary paper on mobilities has been published.[12a]

The much applied (perhaps over applied) distribution coefficient theory of Overton and Meyer has been considered only incidentally with reference to the action of these substances.[13] That the distribution coefficient (in its true physical sense) between lipoids and water can have no significance in the action of these substances is shown clearly from a study of their properties. One example may be cited illustrating this. In the stoppage of the nerve impulse from the motor nerve to the muscle tissue (curare action) the effectiveness of the tetra methyl and tetra ethyl ammonium ions stands in the ratio of 1 to 25.[14] Tetra propyl ammonium ion stands in its activity intermediate between the methyl and ethyl. With regard to the stimulating effect on the inhibitory mechanism to the heart, etc. (muscarine action) and the stimulating effect on the ganglion cells of the sympathetic system (stimulating nicotine effect) the ethyl derivative is inert, while the methyl derivative gives

[8] Ergebunisse der Physiologie, I, II, 197 (1902).

[9] Archiv. f. exp. Path. & Pharmacol., *58*, 1 (1907).

[10] G. Bredig, *Z. f. physikal. Chem., 13*, 289 (1894).

[11] A. E. Hill, *J. A. C. S., 32*, 1190 (1910).

[12] Hunt and Renshaw, *J. Pharm. and Exp. Therap., 25*, 315 (1925).

[12a] I. Bencowitz and R. R. Renshaw, *J. Am. Chem. Soc., 47*, 1904 (1925).

[13] Overton, *Z. f. physikal. Chem., 22*, 189 (1897). See Heffter's "Handbuch der Exper. Pharmakol.," Vol. 1, p. 565.

[14] Boehm, "Arch. f. experim. Pathol. u. Pharmakol.," *63*, 177 (1910).

these actions strongly. On the other hand, both the methyl and ethyl derivatives in larger doses gives the paralytic nicotine action on the ganglion cells.[15]

Attempts have been made to connect up the chemical properties of certain of these compounds of the choline type with the duration or evanescence of their physiological action.[16] The suggestion seemed wholly warranted from a comparison of the physiological activity with their stability toward excess of alkali as determined in a rough-quantitative way. It was found, for instance, that acetyl choline,

$$(CH_3)_3-\underset{\text{x}}{\underset{|}{N}}-CH_2\ O\ Ac,$$

lowers the blood pressure powerfully, but the action is very evanescent. In alkaline solution it was hydrolyzed apparently quite rapidly. The nitric ester, $(CH_3)_3-\underset{\text{x}}{\underset{|}{N}}-CH_2-CH_2-ONO_2$, and the ethyl ether, $(CH_3)_3-\underset{\text{x}}{\underset{|}{N}}-CH_2-CH_2-O\ Et$, also gave a marked depressor effect. The action was less strong but more prolonged. These compounds showed a much greater resistance to alkali.[17]

From results obtained by Mr. Bacon and the writer[18] in a careful study of certain of the esters and ethers of choline and their analogues it seems incredible that either the rates of hydrolysis or any other conceivable decomposition can have any material bearing on the duration of the muscarine action of these substances. This investigation took up particularly the relative tendency for the onium structure to dissociate and the rates of hydrolysis at a constant pH of 7.8, very slightly higher than that of blood (7.4), and at 37° C. Under these conditions acetyl choline is remarkedly stable toward hydrolysis. Only one seventh was hydrolyzed after three and one half hours. The sulfur acetyl formo choline $(CH_3)_2$ $S-CH_2O$ Ac, having not more than about one six hundredth the depressor effect and not greater evanescence was hydrolyzed approximately 125 times as rapidly. The nitric ester was hardly hydrolyzed at all after 150 minutes. Taken as a whole, the results showed that some derivatives did and some did not follow the principle suggested by Dale. While it is true that the conditions under which these rates of hydrolysis were determined are similar to those in the blood only in regard to the effective concentration of hydroxyl ion and temperature, and while it is conceivable that the order of the rates of hydrolysis by an esterase on these derivatives might be different from the order of the rates of hydrolysis by the hydroxyl ion, still, so far as the writer is aware, there is no case known where the rate of hydrolysis of an ester by an enzyme is appreciably greater than the rate by which the same will be hydrolyzed by hydroxyl ion. To explain, then, the evanescence action of acetyl choline by rapid hydrolysis due to an esterase, it would be necessary to assume an unheard-of rate for the esterase as compared with hydroxyl ion, as well as very greatly different rates for *similar* acetic acid esters.

In order to explain this variation in duration of the action it is necessary to assume, after some factor (as spacial configuration) making possible a selective adsorption has come into play,[19] some other factor or factors determining the varied rates at which these different substances exert their action on the same element of the nervous system.[20]

The well-known hypothesis of Clowes,[21] which suggests that the changes in permeability of protoplasm involves the varied tendencies of the ions of different electrolytes to reverse the phases of the natural emul-

[15] Dale, *Journ. Pharm. and Exp. Therap.*, *6*, 417 (1914–5).

[16] Dale, Ref. No. 5. See also, Ewins, *Biochem. Journ.*, *8*, 44 (1914); Fourneau and Page, Bull. Soc. Chem., *15*, 544 (1914).

[17] It was this same consideration, wholly warranted at the time, which earlier led Hunt and Menge to a study of the preparation of acetyl derivatives of substituted cholines in the hope of obtaining a less readily hydrolyzed ester and, therefore, one giving more prolonged action. They were amply rewarded in obtaining the more stable acetylmethyl choline which when given in a single injection of a few tenths of a milligram kept the blood pressure uniformly lowered to one half of its original value for hours.

[18] A paper describing this work is ready for publication.

[19] As will be shown later, physiological, chemical and physical evidence all point strongly to varied specific adsorptions as being the primal or threshold process involved in the different types of action of these substances. This may or may not be the cause of the varied duration of the same action. Whether or not the varied action is due to differences in physical properties or (and) to different spacial configuration of the drugs and to different structures or (and) environment of the tissue at the seat of action are the real fascinating questions in this interesting problem.

[20] There may be involved differences of rates by which another substance is displaced by these materials through adsorption. Many such cases are known. As Reid Hunt has recently suggested a factor which also should be considered is the rapidity with which the substances are excreted. Some may get out of the blood through the kidneys much more rapidly than others.

[21] G. H. A. Clowes, *J. Phys. Chem.*, *20*, 407 (1916).

sions, has been extended (?) to explain the stimulation or blockage of the nerve impulse brought about by a particular drug.[22] It seemed impossible to apply the theory to explain the action of these onium ions, at least, unless there is interposed some selective threshold process. These ideas were especially attractive on account of their simplicity and apparent reasonableness. Seifriz,[23] however, in a study of systems which probably more nearly approach the natural ones, has shown that the phenomena are not so simple as they were first thought to be. This fact, nevertheless, may be a fruitful discovery, since when one takes into account the physiological effects involved one must believe that the factors concerned are distinctly complex. Those who would attempt to explain the action of drugs on the nervous system by an application of simple physical effect would do well to keep in mind the physiological aspects of the problem. In addition to a number of facts already indicated further emphasis on this thought is supplied by the varied action of certain acyl derivatives of choline. As has been indicated the acetyl choline ion, $[(CH_3)_3 - N - CH_2\ CH_2O\ Ac]^+$, powerfully stimulates the action of the inhibitory nerves to the heart by an action on the endings of these nerves to that organ. The chloro and phenyl acetyl choline ions[24] also stimulate the same inhibitory nerves to the heart, but the seat of the action with them is in part in the brain instead of on the heart. That is, with these very similarly constituted ions, the action has been shifted to a considerable degree to a part of the same nerve in the brain.

Some of the most interesting suggestions that have been made in recent times concerning the mechanism of the nervous impulse have involved connecting up varying concentrations of hydrogen ions with varying permeability.[25] We are not in a position yet to discuss the bearing of our results on these suggestions.

One finds if anything even more striking similarities and dissimilarities in the physiological actions of the methyl and ethyl onium ions of nitrogen, sulfur, phosphorus, arsenic and antimony[26] than of some of the simple inorganic ions. It seems obvious that the strange difference found in the latter class (as, for example, Na^+, K^+ and NH_4^+) can be explained fully only when the structure of these ions has been elucidated. At present this field of knowledge is too speculative to warrant an attempt to apply it. Nevertheless, it is not inconceivable that the structural factor or factors causing these differences in the action of the inorganic ions may be so magnified in the onium ions as to be evaluated. In cooperation with Dr. W. P. Davey an investigation has been started to determine if a relationship can be found with such structures as can be adduced from X-ray studies.

It has long been thought that the onium element, per se, had no determining significance qualitatively in the curare action. That this was based in part on erroneous experimental evidence seems clear from Hunt's recent results[27] showing that the tetra methyl onium ions of arsenic and antimony do not give this effect in the relatively high concentrations used. (A great many different substances give the curare effect in extreme concentrations.) Evidence from the present investigation shows clearly that for the muscarine effect also the onium element is inconsequential qualitatively. We have prepared the phosphorus analogue of choline, $(CH_3)_3 \overset{P}{\underset{Cl}{}} CH_2CH_2OH$, and Hunt has shown that it gives the typical muscarine effect of choline. Moreover, on acetylation of this product a much increased action was found by Hunt, just as he had earlier shown that this occurs with choline itself. The acetyl sulfur formocholine ion $[(CH_3)_2\ S\text{–}CH_2O\ Ac]^+$, too, like the acetyl choline, gives this action more strongly than does choline.

It is clear from the previous statement concerning the properties of the methyl and ethyl derivatives of nitrogen that the character of the alkyl group has great significance. This was shown also a number of years ago by Hunt and Taveau[28] in an examination of over seventy homologs of choline. They found that when other alkyl groups were substituted for the methyl groups in the choline structure the muscarine effect on the blood pressure was either absent or only slightly developed. Hunt at that time suggested that the rôle of the group, $(CH_3)_3 - N - CH_2 - CH_2 - O$ (with X on the N) "is probably to carry the compounds to definite cell struc-

[22] J. S. Hughes and H. N. King, SCIENCE, *57*, 590 (1923); but see, also, Alexander Forbes, *ibid.*, *58*, 49 (1923).

[23] W. Seifriz, SCIENCE, 57, 696 (1923); *Am. J. Physiol.*, 66, 124 (1923).

[24] Hunt and Taveau, Hygienic Laboratory Bull., *73*, 28 (1911); Hunt and Renshaw, Ref. No. 13.

[25] Dorothy Haynes, *Sci. Progress*, 18, 223 (1923); E. Q. Adams, *J. Phys. Chem.*, *26*, 639 (1922); R. S. Lillie, *Physiol. Review*, 1922, p. 2; further references will be found in these papers.

[26] The ethyl derivative and many important methyl derivatives of the last four elements either have not been investigated adequately heretofore or not at all. A number of these are now being prepared and studied.

[27] Hunt and Renshaw, Ref. No. 13.

[28] Hunt and Taveau, Hygienic Laboratory Bull., *73*, 1911, U. S. Public Health Service.

tures or, to use the comparison of Ehrlich, to make them fit in a certain mosaic . . . ."

It would seem from the data now available that the least unsatisfactory working hypothesis is that the initial or threshold process in the action of these compounds involves a selective adsorption due to definite spacial configuration of at least a part of the onium ion.

Several papers will appear shortly describing the synthesis, chemical properties and physical effects of a number of these onium compounds.

SUMMARY

(1) An outline is given of an extended, cooperative investigation now being made on the basis for the physiological activity of onium compounds on the nervous system.

(2) Evidence has been obtained which shows that the process is much less simple than is indicated by a number of theories that have been advanced to explain drug action.

(3) It would appear that the action of these substances is not due either to their chemical decomposition, their activity as bases or to their distribution coefficients. The mobility of their ions is not, at least, of primary significance. To be physiologically active, these substances must exist in the body fluids as cations.

(4) Indirect evidence is given of the necessity of taking into account the probable differences of structure of the mechanism of the nervous system on which these substances act, or (and) the environment at the seat of action.

(5) The probability that the first determining factor in the action of these compounds is something in the nature of a selective adsorption depending on the spacial configuration of the groups involved in the ion structure is suggested.

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SOME FACTS IN THE LIFE OF THOMAS NUTTALL

THE sketches of Thomas Nuttall afford nice evidence of the persistence of error. Nearly all of them repeat mistakes either relative to his journey up the Missouri or about his return from his transcontinental trip.

The first and still the most extended sketch of his life was written by Elias Durand and read March 16, 1860, before the American Philosophical Society and published in their Proceedings, Volume 7, pp. 297 to 315. Durand places the trip up the Missouri in 1910 and dates his return to Boston from California in October, 1835.

The next significant article, anonymously appearing in the *Popular Science Monthly,* Vol. 46 (1895), pp. 689 to 696, seems to be entirely dependent on Durand and to repeat his mistakes. About the same time appeared the article in the Dictionary of National Biography; here the Missouri expedition was correctly dated, but a new variant was introduced in dating Nuttall's arrival in America in 1807; elsewhere the date is given as 1808.

The American Encyclopedia gave the date of the Missouri trip as 1810. The article in the *Popular Science Monthly,* Vol. 4, pp. 52 to 57, gives the correct date for the Missouri trip but repeats for the most part the vague or incorrect statements of Durand.

Curiously enough, precision in both cases is possible because journal accounts have been published both of the Missouri trip and of the return from California. Still more curious, the error in the Missouri date is due to Nuttall's own inaccuracy, thrice repeated in his autobiographical notes found in his geological (not geographical, as given by Durand) structure of the Valley of the Mississippi, a paper read in December, 1820, and printed in the *Journal* of the Academy of Natural Sciences, Vol. I, pp. 14 to 52. Nuttall presumably depended on his memory, in this case in error by a year. On page 24 he writes: "While ascending the Missouri in the summer of 1810." Again on page 31: "On our voyage up the Missouri in 1810." Again on page 52: "Which Mr. Bradbury and myself examined in 1810," referring to the red granitic rock seen in the vicinity of the Sioux River.

This last remark serves beyond any doubt to identify this ascent of the Missouri as that taken with the Astor party. Now of this trip we have Bradbury's account, "Travels in the Interior of America," in the years 1809, 1810, 1811, second edition, London, 1819; reprinted in "Early Western Travels," Vol. V, 1904; also Brackenridge's account, "Journal of a Voyage up the Missouri" performed in the year 1811, second edition, Baltimore, 1816; also reprinted in "Early Western Travels," Vol. VI, 1904. There is, besides, Irving's "Astoria," based on the narratives of Bradbury and Brackenridge and the journals and documents of the Astor party itself.

From these accounts it is clear that Nuttall and Bradbury left St. Louis early in January, 1811 (not 31 December, 1809, as in Durand). Bradbury and