tific topics; II. Short original articles; III. News; IV. Applied science; V. Miscellaneous; VI New books, and VII. Abstracts of scientific articles.

ON behalf of the committee of the Joseph Henry Fund of the National Academy of Sciences the following grants have been made: $575 to Professor A. Franklin Shull, of the department of zoology, University of Michigan, to be used for the purchase of an automatic calculating machine for his researches on the developmental processes and embryonic determination in aphids, and $400 to Dr. Dorothy Wrinch, visiting lecturer in the department of chemistry of the Johns Hopkins University, to defray the expenses of computations involved in the interpretation of x-ray data in the study of the structure of certain protein molecules, particularly insulin and lactoglobulin.

SIR JOHN SIMON announced in the House of Commons recently, according to the London *Times*, that Parliament would be invited in the estimates, shortly to be presented, to maintain the provision made for the universities and colleges at the existing level—namely, £2,149,000. He added that the government was fully conscious of the vital part played by the universities in the national life and of the importance of maintaining the standards of university education as far as possible in the strained conditions of war. He was satisfied that the maintenance of the present financial provision was necessary if the universities were to continue to make their essential contribution in various ways to the present national effort. Local authorities, he hoped, would take similar action.

THE *Australian Journal of Science* announces that by an arrangement between the government and the University of Adelaide, the Adelaide Observatory is to become more closely associated with the university. It is expected that its present site will be made available for the Adelaide Boys' High School. A new building is to be provided for the observatory within the university grounds adjacent to the Physics and Engineering Building. The government astronomer, G. F. Dodwell, will be in charge, and it is expected that cooperation between the observatory and the physics department will allow students in physics to receive some teaching in astronomy.

DISCUSSION

RELEASE OF ACETYLCHOLINE BY SYMPATHETIC GANGLIA AND SYNAPTIC TRANSMISSION

EXPERIMENTS performed by the writer[1] on the release of acetylcholine by the superior cervical sympathetic ganglion and the nodosum ganglion of the vagus nerve have yielded results that differ in important details from those previously reported by Feldberg and Vartiainen.[2] The problem of the release of acetylcholine by these structures has again been investigated by MacIntosh,[3] and in making reference to his work, Sir Henry Dale[4] has recently remarked that the validity of the fundamental observation made by Feldberg and Vartiainen, although challenged by me, has been effectively reinstated by MacIntosh, whose evidence "must stand until it has been directly answered." The discussion which follows will show that MacIntosh's results do in fact disagree with some of my own findings, but that they also disagree with results previously obtained in the same laboratory by Feldberg and his collaborators.

At the start of the artificial perfusion of the superior cervical ganglion, and in the absence of stimulation and of peripheral response, there may appear significant outputs of A.Ch., which do not prevent the prompt appearance of a peripheral response upon stimulation of the preganglionic trunk. Initial spontaneous outputs had occasionally been observed by Gaddum and Feldberg[5] and had been described by Brown and Feldberg[6] in these words: "The venous effluent at the beginning of the perfusion of a ganglion with an eserinized Locke solution often contains some A.Ch., the concentration being rarely higher than 0.01 γ per cc. The concentration decreases regularly and A.Ch. has usually disappeared after less than 30 min. perfusion." In a subsequent paper Brown and Feldberg[7] report that after several minutes of stimulation, synaptic transmission with a well maintained peripheral response is accompanied by the release of A.Ch. by the ganglion in the concentration of 0.01 γ per cc. Therefore, the existence of "spontaneous" outputs of A.Ch. in similar concentrations, but without synaptic transmission, must be regarded as significant. In my early experiments, in which the ganglion was prepared for perfusion according to the technique described by Gaddum and Feldberg and Feldberg and Vartiainen, initial spontaneous outputs as described by these investigators were observed, but later, after improvements in the technique of dissection of the ganglion had been introduced,[8] the initial spontaneous outputs of A.Ch. became very small or even failed to appear. In MacIntosh's experiments the concentration of A.Ch. in the

[1] R. Lorente de Nó, *Amer. Jour. Physiol.*, 121: 331, 1938.
[2] W. Feldberg and A. Vartiainen, *Jour. Physiol.*, 83: 103, 1934.
[3] F. C. MacIntosh, *Jour. Physiol.*, 94: 155, 1938.
[4] H. Dale, SCIENCE, 90: 393, 1939.
[5] J. H. Gaddum and W. Feldberg, *Jour. Physiol.*, 81: 305, 1934.
[6] G. L. Brown and W. Feldberg, *Jour. Physiol.*, 86: 290, 1936.
[7] *Ibid.*, 88: 265, 1936.
[8] R. Lorente de Nó, *op. cit.*, p. 336.

initial spontaneous output, when there was any, was very small.

In some of the experiments made with the improved technique of dissection of the ganglion, preganglionic stimulation resulted in an output of A.Ch. in concentrations several times smaller than those I had observed in perfusions performed by the original technique.[9,10] In fact, in one instance the output of A.Ch., if any had taken place, was so small that it did not reach the threshold of the leech preparation that was being used. For this and other reasons given in the original paper the conclusion was reached that initial spontaneous output of A.Ch. and its release in amounts larger than those observed at the start of successful perfusions, was a pathological phenomenon. Taking the last experiment as a paradigm, it may be said that the upper limit of the amount of physiologically released A.Ch. could not be more than 4×10^{-12} gm A.Ch. per maximal shock delivered to the preganglionic trunk. In the case of striated muscle, Fleisch, Sibul and Kaelin[11] had concluded that the release of A.Ch. was altogether pathological, but in the case of the ganglion I did not consider the evidence sufficient to conclude that even the release of A.Ch. in the small amounts obtained was pathological. At present, however, in view of the results obtained by MacIntosh, it seems probable that some degree of abnormality is always required for the release of A.Ch. in any amount. As this is an important point, a somewhat detailed discussion will be made.

A comparison of the experiments performed by the London school with my own experiments reveals that as technical improvements were introduced in the perfusion of the ganglion, the amounts of A.Ch. released by preganglionic stimulation decreased progressively. In 1934, Feldberg and Vartiainen reported that preganglionic stimulation resulted in the output of 100×10^{-12} to 66×10^{-12} gm of A.Ch. per shock delivered to the preganglionic trunk. But in 1938, by the use of diluted blood as a perfusion fluid, MacIntosh found that in 24 out of 26 stimulations, the output per shock was between 15×10^{-12} and 35×10^{-12} gm, with a mean of 24×10^{-12} gm. In the other two cases the outputs per shock were 8×10^{-12} and 53×10^{-12} gm respectively. In my own early experiments I observed a release of A.Ch. in concentrations so strong that the output per shock must have been as large as, if not larger than the largest figure of Feldberg and Vartiainen. With increasing experience in the preparation of the ganglion, and still using Locke's solution as a perfusion fluid, the concentration of A.Ch. in the output decreased significantly. In experiment XIX, in which the histological analysis revealed severe damage of the ganglion, the outputs per shock during the first three periods of stimulation respectively were 66×10^{-12}, 58×10^{-12} and 40×10^{-12} gm, *i.e.*, amounts comparable to those reported by Feldberg and Vartiainen. In contrast, in experiments XVIII and XX, in which the subsequently made histological analysis failed to show any significant alteration of the ganglia, the outputs were: Experiment XVIII, 14×10^{-12}, less than 2.3×10^{-12} and 14×10^{-12} gm; and Experiment XX, 4×10^{-12}, 4×10^{-12} and 10×10^{-12} gm, *i.e.*, on the average outputs equal to the minimal output reported by MacIntosh.

For experiments performed with blood-perfused ganglia, Feldberg and Vartiainen reported that preganglionic stimulation causes the release of A.Ch. in concentrations "well within the range of those obtained with the saline effluent of an artificial perfusion." The importance of this finding was emphasized by its being presented as a conclusion: "Preganglionic impulses liberate acetylcholine in the ganglion with natural circulation, as in that artificially perfused." Brown and Feldberg[12] report that in the case of blood-perfused ganglia the concentration of A.Ch. released by continued preganglionic stimulation is maintained almost unchanged, while in the case of ganglia under artificial perfusion the concentration of A.Ch. shows a sharp decline soon after the start of the persistent stimulus. MacIntosh's results were different, because he reports that in blood-perfused ganglia the output of A.Ch., when present, was small, and A.Ch. failed to appear in three out of five experiments. MacIntosh specifically states that in the two positive experiments the concentration of A.Ch. was "well below that found in the perfusion experiments"; and further: "Dr. G. L. Brown informs me that in subsequent experiments of this kind, which he made with Dr. Feldberg in another connection, positive results were not obtained in all cases, in conformity with my own results." MacIntosh also states: "It may, therefore, be regarded as not improbable, that some degree of departure from perfectly normal conditions may be required to enable A.Ch. liberated at the synapses on the ganglion to escape into the circulation so as to be detected in the fluid leaving the vein." In regard to the last statement, however, the present writer believes that if A.Ch. did not escape, even when "it could be shown that the blood contained sufficient eserine to preserve A.Ch.," then there is no proof that A.Ch. was set free outside the synaptic endings to stimulate the ganglion cells.

In some of my experiments it was observed that the passage of impulses through the nodosum ganglion of the vagus resulted in the release of A.Ch. In MacIntosh's experiments this release was not observed.

[9] W. Feldberg and A. Vartiainen, *op. cit.*

[10] J. H. Gaddum and W. Feldberg, *op. cit.*

[11] A. Fleisch, J. Sibul and M. Kaelin, *Arch. Internat. Physiol.*, 44: 24, 1936.

[12] G. L. Brown and W. Feldberg, *Jour. Physiol.*, 88: 275, 1936.

But working with excised vagus nerves and ganglia, Lissák[13,14] reports a regular release of A.Ch. Apparently, excision creates a greater degree of departure from normal conditions than does perfusion. Be that as it may, Lissák's results lend strong support to my conclusion that the A.Ch. metabolism is a process that is not specific to synaptic junctions.

The results obtained by Lissák may have invalidated my conclusion that entrance into the ganglion cells of impulses conducted in the antidromic direction may result in the release of A.Ch., if the proper conditions for the release have been created. When the postganglionic trunk is stimulated, the escape of the stimulus to the preganglionic trunk is easily prevented, but not escape to the neighboring nerve trunks. Consequently, as the stumps of the X and XII nerves are included in the perfused mass of tissue, the possibility exists that the "antidromic" A.Ch. actually was released by the cut ends of these nerves. This explanation would undoubtedly be adequate, but it would become necessary only if the existence of A.Ch. in ganglion cells should be disproved. Brown and Feldberg[15] report that ganglion cells contain some A.Ch. This statement is denied by Lissák,[16] although Loewi and Hellauer[17] found some A.Ch. in the postganglionic trunk.

Whether the A.Ch. that may be released by preganglionic stimulation is released only, or at least chiefly, at the synapses, has not been demonstrated up to the present time. Direct proof of the synaptic origin was believed to have been obtained in blocking experiments.[18] However, a fundamental, but apparently little known observation of de Castro[19] has demonstrated that nicotine does not paralyze the ganglion cells, but does act on the presynaptic fibers. Therefore, the release of A.Ch. during the nicotine block proves that at least a part of the A.Ch. is released by the presynaptic fibers, and consequently no proof exists that synapses are a more generous source of A.Ch. than the rest of the presynaptic fiber.

Another point under discussion is whether the release of A.Ch., when it does take place, follows the temporal course of synaptic transmission. When using the original technique for the perfusion of the ganglion,[20,21] in several experiments I found, in agreement with Feldberg and Vartiainen, that A.Ch. was released or its output increased only during the periods of stimulation of the preganglionic trunk. But later with the use of the new technique I found, this time in agreement with observations made by Barsoum, Gaddum and Khayyal,[22] that the output of A.Ch. may considerably outlast stimulation and synaptic transmission. MacIntosh did not observe delayed outputs of A.Ch. and interprets the delayed output in my experiments as a delayed removal of A.Ch. that had been released during stimulation. Without further experimental evidence this question can not be definitively settled; nevertheless, it must be remarked that if the delayed outputs of A.Ch. should have been due to delayed removal, then no significant immediate outputs would have been observed in my experiments, while in fact immediate and delayed outputs were repeatedly observed in the same experiment, the immediate outputs often being the larger.

In conclusion, the fundamental observation of Feldberg and Vartiainen, which has been considered as the direct proof of the chemical theory of synaptic transmission,[23] included several essential points: A.Ch. is released in given amounts at the preganglionic synapses when these are activated by nerve impulses, and the release also takes place in blood-circulated ganglia. The release occurs only at the synapses and only during synaptic transmission. But from later work reviewed in this discussion it appears that A.Ch. is not regularly released by blood-circulated ganglia, but is released only after a certain departure from normal conditions has been created and then in extremely variable amounts. Synaptic transmission is, therefore, possible without the release of any A.Ch., and also with its release in large amounts. The liberation of A.Ch. is a process that is not specific to the synapses and there are experimental results which indicate that it may take place after transmission has been effected. These recently established facts do not diminish the importance of the discovery of A.Ch. metabolism in sympathetic ganglia and other nervous structures. But they make it advisable to consider whether A.Ch., instead of being the synaptic transmitter, actually plays a less specific role in the course of the electrochemical reactions that take place during transmission of nerve impulses and subsequent processes of recovery.

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[13] K. Lissák, *Amer. Jour. Physiol.*, 126: 564, 1939.
[14] *Ibid.*, 127: 263, 1939.
[15] G. L. Brown and W. Feldberg, *op. cit.*, p. 265 ff.
[16] K. Lissák, *Amer. Jour. Physiol.*, 127: 263, 1939.
[17] O. Loewi and H. Hellauer, *Pflügers Arch.*, 240: 769, 1938.
[18] H. Dale, *op. cit.*
[19] F. de Castro, *Trav. Lab. Rech. biol., Madrid*, 31: 271, 1936–1937.
[20] W. Feldberg and A. Vartiainen, *op. cit.*
[21] J. H. Gaddum and W. Feldberg, *op. cit.*
[22] G. S. Barsoum, J. H. Gaddum and N. A. Khayyal, *Jour. Physiol.*, 82: 9, 1934.
[23] H. Dale, "Harvey Lectures," 229 pp., 1936–1937.

POSTSCRIPT TO "ROGER BACON WAS MISTAKEN"

MY brief article in the March 29 issue of SCIENCE, though needing no modification, would have been much