NUMBER 3
JANUARY 15, 1979

This Week's Citation Classic

Chappell J B. Systems used for the transport of substrates into mitochondria. *Brit. Med. Bull.* **24:** 150-7, 1968.

This short review describes the evidence for the existence of specific substrate transporting systems in mitochondrial membranes. A discussion of the probable metabolic role of these carriers is given. [The *SCI*® indicates that this paper was cited 256 times in the period 1968-1977.]

J. B. Chappell
Department of Biochemistry
University of Bristol Bristol,
BS8 1TD, United Kingdom

January 23, 1978

"This paper, which is a short review, represented some of the thoughts which were in my colleagues' and my minds at that time. The realization of the existence of the mitochondrial substrate translocators came from experiments performed as a consequence of two sets of observations. One was the catalytic effect of malate on the oxidation of isocitrate by substrate-depleted liver mitochondria; the other some work by Tony Crofts and me on the permeability of mitochondria to phosphate, inferred from studies on cation transport. I had never been happy with my (mis) interpretation of the catalytic effect of malate, and the work with Crofts indicated that, apart from phosphate, small anions were unable to permeate mitochondria. Older work with Guy Greville on the latency' of mitochondrial rhodanese (thiosulfate transulfurase) also indicated that small anions may not be able to penetrate mitochondria. Since it was known that most of the dehydrogenases and other enzymes dealing with the metabolism of anions were located in the mitochondrial matrix, this impermeability posed a real problem.

"The major part of the new experimental material referred to in the paper was known at the end of one day's work by a graduate student, Keith Haarhoff, and myself. The morning of that day was spent in making up iso-osmotic solutions of the ammonium salts of various anions. Mitochondrial swelling was followed with a crude but effective home-made light-scattering apparatus. The first experiments were disappointing; mitochondria swelled very well in phosphate (which we already knew) but not in malate or citrate. Was the failure to swell in malate due to some effect of large amounts of malate? Was the phosphate carrier inhibited in the presence of malate? Addition of even small amounts of phosphate to mitochondria suspended in isoosmotic ammonium malate produced an unexpectedly large amount of swelling. Phosphate appeared to be necessary for malate permeation It was a short step to show that malate allowed citrate entry (when phosphate was present). The ground-work was laid

"The discovery that glutamate was necessary for aspartate permeation into liver mitochondria was made by Angelo Azzi while he was working in Bristol, and was due to an error! Repeated attempts to oxidise intramitochondrial NAD(P) which had been reduced by oxoglutarate (in the presence of malonate) by addition of aspartate had failed; the oxidation was expected since oxaloacetate would be generated in tramitochondrially by transamination. On one occasion the experiment 'worked'; however, glutamate had been added after aspartate instead of more aspartate as was intended. The two tubes stood in ice side by side, and in the gloom required for the proper running of the spectrophotometer, Azzi erred "