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This Week's Citation Classic®

Humphrey J H & Jaques R. The release of histamine and 5-hydroxytryptamine (serotonin) from platelets by antigen-antibody reactions (*in vitro*). *J. Physiology* **128**:9-27, 1955.
[National Institute for Medical Research, Mill Hill, London, England]

Rabbit platelets contain large amounts of histamine and serotonin, which are released from platelets in heparinized plasma containing antibody on addition of antigen. Release required free Ca^{++} and some factor(s) present in normal plasma. Antigen-induced release was not due to thrombin or plasmin activation. It was inhibited in plasmas from hyperimmunized rabbits, which contained high levels of trypsin inhibitor. Release of serotonin on addition of antigen from human, dog, and guinea pig platelets occurred similarly, but anaphylaxis in guinea pigs was unaffected by platelet deprivation. [The *SCI*® indicates that this paper has been cited in over 325 publications.]

John H. Humphrey
Department of Immunology
Royal Postgraduate Medical School
Hammersmith Hospital
London W12 0HS
England

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The origin of these experiments was an observation that reversed passive Arthus reactions were diminished by cortisone but the only evident difference from control reactions was a lesser local invasion by granulocytes. At that time, histamine was considered to be the agent that triggered acute inflammation, so we supposed that histamine would be carried in these cells. (Its concentration in basophils had not yet been discovered.) When we tested blood from various species, it was apparent that neutrophils contained little or no histamine but that rabbit platelets (exceptionally) contained a lot. Platelets from the seven species examined also contained some serotonin, though only rabbit, goat, and cat contained much. This meant that the hypothesis about the mechanism of Arthus reactions was wrong and led to separate experiments whose results showed that granulocytes were essential for the inflammatory response to occur. However, F.C. McIntire and colleagues had reported that histamine was released from the blood of rabbits sensitized to egg white when incubated in the presence of antigen,[1] so we decided to examine the behaviour of platelets in a more defined system.

I did not expect that this paper would become a *Citation Classic*, and it was certainly not the one that I reckoned the most important that I wrote. We did not really discover what was the mechanism whereby the platelets became activated—and I am not sure that anyone has discovered this since. Although we toyed with the idea that complement was involved, this was not compatible with partial retention of plasma activity after heating at 56° C. Various treatments that induced anaphylatoxin in normal plasmas also caused histamine release. Platelets have since been reported to become aggregated (and presumably to release mediators) by C3a and C5a in a Ca^{++}-dependent manner,[2] which fits with our observations. Barbaro a few years later[3] found that, whereas heating plasma for 30 minutes at 56° C partly diminished antigen-dependent histamine release, heating at 44° C actually increased it. This is not inconsistent with generating anaphylatoxin, and, in view of the rather large amounts of antibodies used, I think retrospectively that anaphylatoxin production was probably what we were looking at.

Except as a possible model, interest in platelets among immunologists—though not among pathologists—declined sharply after it became recognised that basophils were the main source of histamine and several other active agents in anaphylactic reactions (except perhaps in the rabbit), and that basophils are sensitized by IgE antibodies, for which they have specific high-affinity receptors. However, interest has recently revived since the discovery of a second type of receptor for IgE on monocytes, eosinophils, and platelets. Although these receptors are of relatively low affinity, when IgE is dimerized or in complexes with antigens, these bind to and can trigger these cells.[4] Platelets activated in this way can even kill schistosomes—but they do this by means of oxygen metabolites rather than serotonin.

My coauthor, Roland Jaques, died some years ago. As a side issue, I wrote a paper with a pharmacologist, Chai-Chi Toh, which gave the first description of the active uptake of serotonin by platelets.[5] Toh later became vice president of Singapore and combined this office with spending mornings in the lab there!

1. **McIntire F C, Roth L W & Richards R K.** The *in vitro* release of histamine from the blood cells of sensitized rabbits: relationship to blood coagulation mechanisms. *Amer. J. Physiol.* 159:332-6, 1949.
2. **Hugli T E & Müller-Eberhard H J.** Anaphylatoxins: C3a and C5a. *Advan. Immunol.* 26:1-53, 1978. (Cited 235 times.)
3. **Barbaro J F.** The release of histamine from rabbit platelets by means of antigen-antibody precipitates. II. The role of plasma in the release of histamine. *J. Immunology* 86:377-81, 1961. (Cited 50 times.)
4. **Capron A, Dessaint J P, Capron M, Joseph M, Ameisen J C & Tonnel A B.** From parasites to allergy: a second receptor for IgE. *Immunol. Today* 7:15-18, 1986.
5. **Humphrey J H & Toh C C.** Absorption of serotonin (5-hydroxytryptamine) and histamine by dog platelets. *J. Physiology* 124:300-4, 1954. (Cited 120 times since 1955.)

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