is partly located on the exterior surface of the cell and (3) that this component migrates on SDS-polyacrylamide gels in an anomalous fashion, similar to the glycoprotein. I conclude that a polypeptide part of the glycoprotein extends through the cell membrane to the interior surface of the membrane.

Proteins in Membranes

I have previously shown that component *a*, a 105,000 dalton polypeptide, is situated in the lipid bilayer in such a way that different parts of the polypeptide chain reside on opposite sides of the membrane barrier[9]. Component *a* does not rotate in the membrane[9]. Component *b*, the glycoprotein whose molecular weight is about 31,400, of which only one-third is protein[1], seems to be similarly built into the membrane: that part of it carrying the carbohydrate is on the external surface of the cell, while a different part of the same polypeptide chain resides on the inner surface of the membrane. Apart from this similarity in disposition, components *a* and *b* are very different types of molecules: the size of the protein moiety differs by about a factor of ten. The fact that both of them extend through the lipid bilayer—and they seem to be the only major proteins on the surface of the red cell—suggests that most, if not all, membrane proteins which are partly on the external surface of a cell will also extend through the membrane to the inner surface of the lipid bilayer.

This glycoprotein contains about twenty-eight residues of sialic acid per molecule[1], from which one may estimate that there are about 7×10^5 copies of it per cell (provided that some 1.2% of the ghost's mass of 10^{-12} g is sialic acid[13], of which about 70% is present in this glycoprotein[8]). This is very close to my previous estimate of the number of copies of component *a* per cell—about 5×10^5 (ref. 8). Assuming that each is evenly spread out over the surface of the erythrocyte, there must be roughly one of each of component *a* and glycoprotein per 130 Å square.

I thank the Regional Blood Transfusion Service in Cambridge for supplies of fresh blood.

Received April 19, 1971.

1 Winzler, R. J., in *Red Cell Membrane, Structure and Function* (edit. by Jamieson, G. A., and Greenwalt, T. J.), 157 (Lippincott, Philadelphia, 1969).
2 Berg, H. C., *Biochim. Biophys. Acta*, **183**, 65 (1969).
3 Lenard, J., *Biochemistry*, **9**, 1129 (1970).
4 Phillips, D. R., and Morrison, M., *Biochem. Biophys. Res. Commun.*, **40**, 284 (1970).
5 Lenard, J., *Biochemistry*, **9**, 5037 (1970).
6 Bender, W. W., Garan, H., and Berg, H. C., *J. Mol. Biol.*, **58**, 783 (1971).
7 Weber, K., and Osborn, M., *J. Biol. Chem.*, **244**, 4406 (1969).
8 Bretscher, M. S., *J. Mol. Biol.*, **58**, 775 (1971).
9 Bretscher, M. S., *J. Mol. Biol.* (in the press).
10 Shapiro, A., Viñuela, E., and Maizel, J. V., *Biochem. Biophys. Res. Commun.*, **30**, 240 (1967).
11 Zacharius, R. M., Zell, T. E., Morrison, J. H., and Woodlock, J. J., *Anal. Biochem.*, **30**, 148 (1969).
12 Weber, K., *Methods in Enzymology* (in the press).
13 Rosenberg, S. A., and Guidotti, G., *J. Biol. Chem.*, **244**, 5118 (1969).

Inhibition of Prostaglandin Synthesis as a Mechanism of Action for Aspirin-like Drugs

J. R. VANE

Department of Pharmacology, Institute of Basic Medical Sciences, Royal College of Surgeons of England, Lincoln's Inn Fields, London WC2A 3PN

Experiments with guinea-pig lung suggest that some of the therapeutic effects of sodium salicylate and aspirin-like drugs are due to inhibition of the synthesis of prostaglandins.

THERE have been many attempts to link the anti-inflammatory actions of substances like aspirin with their ability to inhibit the activity of endogenous substances. Collier[1,2] calls aspirin an "anti-defensive" drug, and is largely responsible for studying its possible antagonism of the activity of endogenous substances such as kinins[3,4], slow reacting substance in anaphylaxis (SRS-A) (ref. 5), adenosine triphosphate[6], arachidonic acid[7,8] and prostaglandin $F_{2\alpha}$ (refs. 2 and 7).

A possible mechanism for some of the actions of anti-inflammatory acids was discovered by Piper and Vane[10] who found that lungs could release a previously undetected substance which, because of its action, they called "rabbit aorta contracting substance" or RCS. When isolated perfused lungs of sensitized guinea-pigs were challenged, RCS, along with histamine, SRS-A, prostaglandin E_2 (PGE_2) and prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) (ref. 11), were released. The release of RCS, which could also be provoked by bradykinin and SRS-A, was antagonized by aspirin-like drugs, as was the evoked bronchoconstriction. Because RCS has a short half-life (<5 min) it has not been isolated and its chemical nature is unknown. However, the finding that arachidonic acid, a prostaglandin precursor which induces bronchoconstriction, also releases RCS from perfused lungs[12] makes it possible that RCS is a prostaglandin or has a structure intermediate between arachidonic acid and PGE_2 or $PGF_{2\alpha}$. This release of RCS and the associated bronchoconstriction are also antagonized by aspirin-like drugs.

Prostaglandin release can often be equated with prostaglandin synthesis[13], for many tissues can be provoked to release more prostaglandin than they contain. The possibility arises, therefore, that anti-inflammatory substances such as aspirin inhibit the enzyme(s) which generate prostaglandins. The experiments described below were designed to test this possibility. Aspirin and indomethacin strongly inhibit prostaglandin synthesis; this may be the mechanism underlying some of their therapeutic actions.

Cell-free homogenates of guinea-pig lung synthesize prosta-

© 1971 Nature Publishing Group

glandins E_2 and $F_{2\alpha}$ from arachidonic acid and the following is based on the procedure of Ånggård and Samuelsson[14]. Lungs from four adult guinea-pigs were excised rapidly and washed in ice-cold medium (a modified Bucher medium containing 20 mM KH_2PO_4, 72 mM K_2HPO_4, 27.6 mM nicotinamide, and 3.6 mM $MgCl_2$; *p*H 7.4). The lung tissue was homogenized in an MSE blade homogenizer at full speed for 1 min with a tissue: medium ratio of 1 : 4. The resultant suspension was transferred to a Potter–Elvehjem homogenizer and further homogenized by six up and down strokes of the 'Teflon' pestle. The homogenate was then centrifuged at 900*g* for 15 min and the supernatant fluid was used. Fresh homogenates were made on the morning of each experiment.

Arachidonic acid was dissolved in ethanol (0.1 ml./mg) and diluted with a 0.2% (w/v) sodium carbonate solution (0.9 ml./mg), thus giving a solution of arachidonic acid of 1 mg/ml. This was further diluted to 200 µg/ml. with the modified Bucher medium.

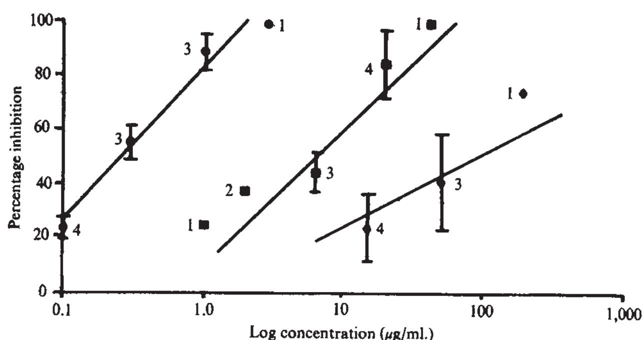

Fig. 1 Concentration (µg/ml.) of indomethacin (●), aspirin (■) and salicylate (◆) plotted on a log scale against the percentage inhibition of prostaglandin synthesis (assayed as $PGF_{2\alpha}$ on rat colons). The lines are those calculated for best fit. Numbers by the points indicate number of experiments. When three or more estimates were averaged, the standard error of the mean is shown.

Flasks containing 10 µg of arachidonic acid (0.05 ml.) and lung homogenate (1 ml.) were incubated aerobically at 37° C with gentle shaking for 30 min. A zero-time sample was taken. The reactions were stopped by heating the flasks in a boiling water bath until the protein in the sample coagulated (30–60 s) and then diluting five or ten-fold with 0.9% (w/v) saline. The samples were frozen if kept overnight, or kept on ice until assayed.

Prostaglandin-like activity was assayed[15] on isolated stomach strips[16] and colons[17] from the rat, superfused[18] in series with Krebs solution containing a mixture of antagonists[19] to make the assay more specific. Activity was assayed by bracketing the contractions induced by injections of diluted samples between smaller and larger contractions induced by the standards. In the dose range used (2–20 ng), PGE_2 contracted the stomach strips, but had no effect on the colons, whereas $PGF_{2\alpha}$ contracted the colons but had a much weaker effect than PGE_2 on the stomach strips. Activity was assayed on the rat colons in terms of $PGF_{2\alpha}$ and on the stomach strips in terms of PGE_2. But because $PGF_{2\alpha}$ had a small effect in the PGE_2 assay and the enzyme preparation also partially inactivated the PGE_2 generated[14], less emphasis has been placed on the PGE_2-like activity assayed in these experiments.

In some experiments, the reactions were terminated by acidifying to *p*H 3 with hydrochloric acid and extracting twice with ethyl acetate. The combined extracts were evaporated to dryness under reduced pressure. The residue was taken up in 0.2 ml. ethanol and chromatographed in the A I system[20] on thin-layer chromatography plates[21] with markers of 5 µg authentic prostaglandin E_2 and $F_{2\alpha}$. The strips on the developed chromatograms corresponding to the marker spots were separated, as was the area in between them. The rest of the chromatogram was divided into 1–3 cm strips. Each section was scraped into a test tube and shaken with 2 ml. Krebs solution. The supernatant was assayed on the rat colons and stomach strips.

The zero-time samples contained (per ml.) 60–150 ng of $PGF_{2\alpha}$-like activity and 120–750 ng of PGE_2-like activity. This activity varied between samples of the same enzyme preparation by less than 5% and did not increase when the enzyme was incubated without arachidonic acid for 30 min. Incubation with arachidonic acid for 30 min increased $PGF_{2\alpha}$-like activity by 220–520 ng/ml. and PGE_2-like activity by 100–500 ng/ml., according to the enzyme preparation. Variation between different control samples of the same preparation was less than 7%.

Tests for Inhibition

Results were expressed as the generation of $PGF_{2\alpha}$ or PGE_2-like activity (30 min sample activity minus zero-time sample activity). To test for inhibition of prostaglandin synthesis, varying amounts of indomethacin, sodium acetylsalicylate, sodium salicylate or other substances were added to the incubation flasks in volumes of 0.1 ml. or less; inhibition of generation by a drug was expressed as the percentage inhibition of the control generation.

Indomethacin, sodium aspirin and sodium salicylate all inhibited the generation of $PGF_{2\alpha}$-like activity. The degree of inhibition varied from one enzyme preparation to another, but with any batch there was a linear relationship between percentage inhibition and log concentration of indomethacin or aspirin. The media used to dissolve the anti-inflammatory substances did not influence prostaglandin synthesis. The results from all experiments are shown in Fig. 1. The ID_{50} for indomethacin was 0.27 µg/ml. (0.75 µM), whereas that for aspirin was 6.3 µg/ml. (35 µM). Thus, on a weight basis, indomethacin was twenty-three times more potent than aspirin as an inhibitor of synthesis of $PGF_{2\alpha}$, and on a molar basis forty-seven times more potent. Sodium salicylate was less potent than aspirin as an inhibitor of synthesis of $PGF_{2\alpha}$-like activity and there was much more variation in the results (Fig. 1). Similar results were obtained when the activity of the samples was assayed on stomach strips in terms of PGE_2.

Hydrocortisone (50 µg/ml.) inhibited synthesis of $PGF_{2\alpha}$ and PGE_2-like activity by less than 20%; morphine (50 µg/ml.) or mepyramine (50 µg/ml.) had no effect. None of the drugs tested decreased the contractions of the assay tissues induced by PGE_2 or $PGF_{2\alpha}$; indeed there was sometimes a small potentiation of the responses.

Two samples (1.0 ml.) of enzyme were incubated without arachidonic acid: 1 µg $PGF_{2\alpha}$ was added to one and 1 µg PGE_2 to the other. After 30 min of incubation, the activity remaining was equivalent to 0.85 µg $PGF_{2\alpha}$ and 0.6 µg PGE_2.

In experiments with two different lung homogenates, samples containing arachidonic acid (10 µg/ml.) were incubated, extracted and the activity was separated by thin-layer chromatography in the A I system as described. In the first experiment, the zones corresponding to the prostaglandin markers showed substantial activity in the control 30 min incubation sample (160 ng $PGF_{2\alpha}$ and 50 ng PGE_2/ml. original sample), whereas the zero time sample showed much less (40 ng $PGF_{2\alpha}$ and 5 ng PGE_2/ml.). Similar samples incubated with indomethacin (5 µg/ml.) or aspirin (40 µg/ml.) showed little or no increase in $PGF_{2\alpha}$ or PGE_2-like activity over the zero-time sample.

In the second experiment, lower concentrations of indomethacin (1 µg/ml.) and aspirin (20 µg/ml.) were used. As Fig. 2 shows, indomethacin reduced the generation of activity in the $PGF_{2\alpha}$ zone to 25% of that in the control incubation but the activity in the PGE_2 zone was only reduced to 78%. With aspirin (20 µg/ml.) activity in the $PGF_{2\alpha}$ zone was reduced to

© 1971 Nature Publishing Group

about 56% and in the PGE_2 zone to 50%. Further identification of the PG-like activity in these experiments was considered unnecessary, for the enzyme system was the same as that used by Ånggård and Samuelsson[13], who identified PGE_2 and $PGF_{2\alpha}$ as the active products of the incubation.

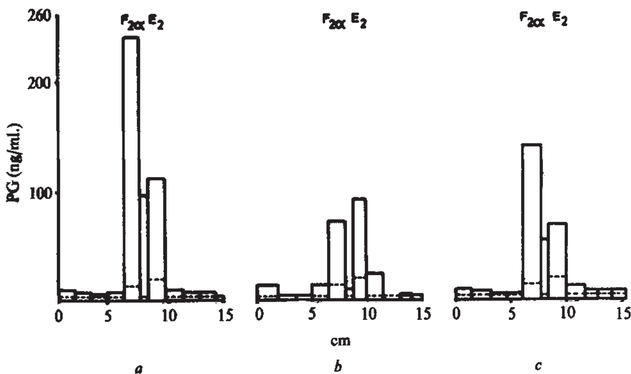

Fig. 2 Prostaglandin-like activity in samples of lung homogenate incubated for 30 min with arachidonic acid (10 µg/ml.), extracted with ethyl acetate and separated by thin-layer chromatography in the A I system. The chromatogram was divided into strips and the zone corresponding to the $PGF_{2\alpha}$ marker was assayed on rat colons in terms of $PGF_{2\alpha}$. The other zones were assayed on stomach strips in terms of PGE_2. The dotted lines represent the amount of PG-like activity in the sample at the start of the incubation. Indomethacin (1 µg/ml.) and aspirin (20 µg/ml.) reduced the generation of $PGF_{2\alpha}$ and PGE_2. *a*, Control; *b*, indomethacin; *c*, aspirin.

The results show that the three anti-inflammatory acids tested inhibit the synthesis of prostaglandins. It is not yet known how the inhibition is brought about. If it is by competition with arachidonic acid for the active site of the enzyme, this might explain why all of these anti-inflammatory substances contain an acidic group. It would also explain why hydrocortisone, an anti-inflammatory substance of a different type, has little or no inhibitory action against the prostaglandin synthesizing enzyme(s).

Correlation with Therapeutic Actions

Anti-inflammatory acids have three principal actions; antipyretic, anti-inflammatory and analgesic. They also antagonize bronchoconstriction and some other smooth muscle contractions induced by substances such as bradykinin[1] and have a tendency to induce gastro-intestinal irritation. Can any of these actions be explained by a direct inhibition of prostaglandin synthesis?

First, we consider antipyretic action. When injected into the third ventricle of cats, PGE_1 induces fever[22,23]. It is the most potent substance yet found with this action, being much more active than 5-hydroxytryptamine, PGE_2 or $PGF_{2\alpha}$; $PGF_{2\alpha}$ has little pyretic activity. The antipyretic substance 4-acetamidophenol does not antagonize fever induced by PGE_1. These facts are compatible with the idea that the rise in temperature in a fever is induced by synthesis and release of RCS or of a known prostaglandin such as PGE_1, either in the temperature-regulating area of the hypothalamus or at a place from which it can reach this area. Anti-inflammatory substances might reduce temperature in a fever by preventing such prostaglandin synthesis. A necessary corollary of such a mechanism of action is that a prostaglandin whose synthesis is inhibited by these drugs does not regulate normal body temperature, which is unaffected by antipyretic drugs.

Anti-inflammatory action can also be explained. An E-type prostaglandin is found in exudate[24] during the secondary phase of inflammation induced by carageenin in the rat. Prostaglandins, identified as a mixture of PGE_1, PGE_2, $PGF_{1\alpha}$ and $PGF_{2\alpha}$, have also been isolated from fluid perfusing the skin of patients with allergic eczema[25]. In rat or man, PGE_1 or PGE_2 injected intradermally induces an inflammatory response[26]. Thus abolition of prostaglandin synthesis by this group of acidic substances may be a basis for their anti-inflammatory action.

Analgesic action is less easily explained. Although PGE_1 and PGE_2 and larger doses of $PGF_{1\alpha}$ and $PGF_{2\alpha}$ induce a weal and flare response similar to that caused by histamine release when injected intradermally in man[26], the only subjective effect reported was a sensation of warmth and a slight itching. It is unlikely, therefore, that any of these prostaglandins mediate skin pain. Thus, unless another untested prostaglandin or RCS is involved, there seems no link between a peripheral analgesic action of the anti-inflammatory acids and inhibition of prostaglandin synthesis.

Prostaglandin infusions, however, induce headache[27], so the relief by aspirin-like drugs of such pain (or of pain induced by inflammation) may be explained by an inhibition of prostaglandin synthesis. Collier[28] develops further the possible link between prostaglandin production and pain.

The anti-bronchoconstrictor action may also be due to inhibition of the synthetic pathway for prostaglandins. We have already shown that challenge of sensitized guinea-pig lungs or injection of bradykinin or partially purified SRS-A into unsensitized lungs induces the release of RCS, PGE_2 and $PGF_{2\alpha}$ (refs. 10 and 11). Because the release of RCS was abolished by anti-inflammatory acids, as was the bronchoconstriction induced by bradykinin and SRS-A (ref. 1), we postulated that RCS may be the mediator of the bronchoconstrictor response. Vargaftig and Dao[12] have shown that arachidonic acid also releases RCS and that the release is inhibited by aspirin-like drugs and we have confirmed this (unpublished work). At the time of our first publication on RCS (ref. 10), we were unsure of the contribution that this substance made to the contractions of the tissues used to assay simultaneously the release of prostaglandins. We have assessed this contribution recently; whereas RCS contracts rat stomach strip, it has much less effect on chick rectum or rat colon (Piper and Vane, unpublished work). Re-examination of the tracings from these experiments shows that aspirin-like drugs not only prevented RCS release but also reduced activity on chick rectum and rat colon, indicative of a reduced output of PGE_2 and $PGF_{2\alpha}$ (see, for instance, Fig. 7 in Piper and Vane[10]).

Prostaglandin $F_{2\alpha}$ is bronchoconstrictor[5,29], so the antagonism of bronchoconstriction induced by bradykinin, SRS-A, arachidonic acid and so on may be due to antagonism of release (which probably means synthesis) of RCS or of synthesis and release of $PGF_{2\alpha}$ or both. The ratio of activities against bradykinin-induced bronchoconstriction (indomethacin 2; aspirin 1, salicylic acid 0.03; ref. 1) certainly fits with the relative lack of activity of sodium salicylate against the formation of $PGF_{2\alpha}$. Until RCS can be stabilized or generated in a pure form, however, its contribution to the process of anaphylaxis and to bronchoconstriction induced by anaphylactic mediators cannot be assessed.

Side Effects

The aspirin-like drugs all induce gastro-intestinal symptoms which may include peptic ulceration[30]. Prostaglandin synthesis and release can be provoked by many different forms of mechanical stimulation, including gentle massage[13]. Contractions of the gastro-intestinal tract churn the contents. It is possible, therefore, that the associated mechanical stimulation of the mucosa leads to synthesis intramurally of a prostaglandin which in some way protects the mucosa from damage. Inhibition of prostaglandin synthesis by aspirin-like drugs would remove this protective mechanism.

Whether inhibition of prostaglandin synthesis accounts for all the activities of the anti-inflammatory acids remains to be

© 1971 Nature Publishing Group

elucidated. Clearly, the blood concentrations[31] of indomethacin in man after an oral dose of 200 mg (7.5 μg/ml. at peak; 3.2 μg/ml. after 4 h), even when 90% binding[31] to plasma proteins is allowed for, are higher than concentrations needed to inhibit prostaglandin synthesis in these experiments.

One fact that needs explanation is the apparent lack of activity of sodium salicylate as an inhibitor of prostaglandin synthesis, for this substance has about the same potency as aspirin in anti-pyretic and anti-inflammatory tests[1]. One possibility is that salicylate is more potent as an inhibitor of synthesis of PGE_1 from dihomo-γ-linolenic acid than it is of the synthesis of PGE_2 from arachidonic acid. Certainly, with the probability of a series of iso-enzymes synthesizing from different substrates various prostaglandins (perhaps including RCS) with widely different pharmacological properties, the number of degrees of freedom is more than sufficient to allow explanation of the variations in potencies and properties within the whole group of aspirin-like substances.

There are several other implications of these results, some of which are listed below. First, inhibition of prostaglandin synthesis, perhaps using a more active enzyme preparation[32] than the one used here, together with different substrates, may provide a simple and rapid primary screen for anti-inflammatory drugs of the indomethacin type. Second, one of the few simple *in vitro* antagonisms shown by aspirin-like drugs is against arachidonic acid-induced contractions of some isolated smooth muscle preparations such as the guinea-pig ileum[7]. This suggests that some of the contractile actions of arachidonic acid may be brought about by an intramural synthesis of a prostaglandin. This problem deserves attention, as does the possibility that bioassay of prostaglandins may be improved by addition of a synthesis inhibitor, such as indomethacin, to the fluid bathing the assay tissues.

There is also the possibility that use of anti-inflammatory acids could be extended to ameliorate conditions thought to be brought about by prostaglandin release. For example, some evidence[33] suggests that release of $PGF_{2\alpha}$ occurs during labour. It may therefore be worthwhile testing an anti-inflammatory acid as an inhibitor of unwanted abortion or miscarriage. It would also be interesting to know whether these drugs reduce the efficacy of the intra-uterine device which may work as a contraceptive through prostaglandin release[34].

These results show that biologists now have a simple means of preventing prostaglandin synthesis and release and thereby assessing the functions of prostaglandins in individual cells or tissues, or in the body as a whole. The conclusions described here are supported by the results discussed in the next two articles[35,36].

I thank Mr N. Pitman for technical help and the Wellcome Trust and Medical Research Council for grants.

Received May 6, 1971.

1 Collier, H. O. J., *Adv. Pharmacol. Chemother.*, **7**, 333 (1969).
2 Collier, H. O. J., *Nature*, **223**, 35 (1969).
3 Collier, H. O. J., and Shorley, P. G., *Brit. J. Pharmacol. Chemother.*, **15**, 601 (1960).
4 Collier, H. O. J., and Shorley, P. G., *Brit. J. Pharmacol. Chemother.*, **20**, 345 (1963).
5 Berry, P. A., and Collier, H. O. J., *Brit. J. Pharmacol. Chemother.*, **23**, 201 (1964).
6 Collier, H. O. J., James, G. W. L., and Schneider, C., *Nature*, **212**, 411 (1966).
7 Jacques, R., *Helv. Physiol. Pharmacol. Acta*, **23**, 156 (1965).
8 Berry, P. A., thesis, Council for National Academic Awards, London, 91 (1966).
9 Collier, H. O. J., and Sweatman, J. F., *Nature*, **219**, 864 (1968).
10 Piper, P. J., and Vane, J. R., *Nature*, **223**, 29 (1969).
11 Piper, P. J., and Vane, J. R., in *Prostaglandins, Peptides and Amines* (edit. by Mantegazza, P., and Horton, E. W.), 15 (Academic Press, London, 1969).
12 Vargaftig, B. B., and Dao, N., *Pharmacology* (in the press).
13 Piper, P. J., and Vane, J. R., in *Prostaglandins* (edit. by Ramwell, P., and Shaw, J.) (NY Acad. Sci., in the press, 1971).
14 Ånggård, E., and Samuelsson, B., *J. Biol. Chem.*, **240**, 3518 (1965).
15 Ferreira, S. H., and Vane, J. R., *Nature*, **216**, 868 (1967).
16 Vane, J. R., *Brit. J. Pharmacol. Chemother.*, **12**, 344 (1957).
17 Regoli, D., and Vane, J. R., *Brit. J. Pharmacol. Chemother.*, **23**, 351 (1964).
18 Gaddum, J. H., *Brit. J. Pharmacol. Chemother.*, **8**, 321 (1953).
19 Gilmore, N., Vane, J. R., and Wyllie, J. H., *Nature*, **218**, 1135 (1968).
20 Gréen, K., and Samuelsson, B., *J. Lipid Res.*, **5**, 117 (1964).
21 Willis, A. L., *Brit. J. Pharmacol.*, **40**, 583P (1970).
22 Milton, A. S., and Wendlandt, S. J., *J. Physiol.*, **207**, 76P (1970).
23 Feldberg, W., and Saxena, P. N., *J. Physiol.* (in the press, 1971).
24 Willis, A. L., in *Prostaglandins, Peptides and Amines* (edit. by Mantegazza, P., and Horton, E. W.), 31 (Academic Press, London, 1969).
25 Greaves, M. W., Søndergaard, J., and McDonald-Gibson, W., *Brit. Med. J.*, **2**, 258 (1971).
26 Crunkhorn, P., and Willis, A. L., *Brit. J. Pharmacol.*, **41**, 49 (1971).
27 Bergström, S., Carlson, L. A., and Weeks, J. R., *Pharmacol. Rev.*, **20**, 1 (1968).
28 Collier, H. O. J., *Nature* (in the press).
29 James, G. W. L., *J. Pharm. Pharmacol.*, **21**, 379 (1969).
30 Goodman, L. S., and Gilman, A., *The Pharmacological Basis of Therapeutics*, fourth ed. (Collier-Macmillan, London, 1970).
31 Hucker, H. B., Zacchei, A. G., Cox, S. V., Brodie, D. A., and Cantwell, N. H. R., *J. Pharmac. Exp. Therap.*, **153**, 237 (1966).
32 Nugteren, D. H., Beerhuis, R. K., and Van Dorp, D. A., *Recl. Trav. Chim. Pays-Bas Belg.*, **85**, 405 (1966).
33 Karim, S. M. M., *Brit. Med. J.*, **4**, 618 (1968).
34 Chaudhuri, G., *Lancet*, i, 480 (1971).
35 Smith, J. B., and Willis, A. L., *Nature New Biology*, **231**, 235 (1971).
36 Ferreira, S. H., Moncada, S., and Vane, J. R., *Nature New Biology*, **231**, 237 (1971).

Aspirin Selectively Inhibits Prostaglandin Production in Human Platelets

J. B. SMITH & A. L. WILLIS*

Department of Pharmacology, Institute of Basic Medical Sciences, Royal College of Surgeons of England, Lincoln's Inn Fields, London WC2A 3PN

Platelets in the blood of volunteers who have taken aspirin can no longer produce prostaglandins.

* Present address: Department of Physiology, Stanford University, Stanford, California 94305.

ASPIRIN reduces the adhesiveness to glass of platelets in citrated plasma[1], reduces platelet aggregation by washed connective tissue fragments[2], and inhibits the second wave of aggregation induced by ADP, adrenaline and thrombin[3–5]. Aspirin also inhibits the release from washed pig or human platelets of permeability factors which differ from 5-hydroxytryptamine and histamine and cause contraction of the guinea-pig ileum[6]. One of these factors could be prostaglandin E_2 (PGE_2). This compound increases vascular permeability[7,8] and contracts guinea-pig ileum[9]. When washed human

© 1971 Nature Publishing Group