

The effect of dapsone in steroid-dependent asthma

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We studied the steroid-sparing effect of dapsone in 10 subjects with chronic asthma in a preliminary open trial. Dapsone was chosen because it inhibits neutrophil function and possesses anti-inflammatory effects in a variety of disorders. The study group consisted of 10 subjects with stable, steroid-dependent asthma, aged 23 to 80 years, with normal glucose-6-phosphate dehydrogenase levels. Average daily baseline prednisone dose ranged from 5 to 60 mg. Dapsone, 100 mg, twice daily, by mouth, was started after a 1-month baseline period. Baseline steroid dose, symptom scores, and daily peak flow rates were compared to the latest available 4-week period of dapsone treatment. Average cumulative monthly prednisone dose was reduced from 428 mg to 82 mg ($p < 0.02$). Five of 10 patients stopped steroids by month 6 and two additional patients by month 13. Two additional patients demonstrated a coincidental 74% reduction in steroid dose, and one patient demonstrated no response. Clinical parameters remained stable despite steroid reduction. These preliminary data suggest dapsone may have steroid-sparing effects in chronic asthma. (J ALLERGY CLIN IMMUNOL 1991;87:710-15.)

As current concepts of the pathogenesis of asthma evolve from a primarily bronchospastic to inflammatory model,¹ research efforts are focusing on drugs that may inhibit airway inflammation. Several drugs with putative anti-inflammatory effects, such as gold salts,²⁻⁵ methotrexate,⁶ and hydroxychloroquine,⁷ have demonstrated promising results in the treatment of severe asthma.

Neutrophils may play a role in the inflammatory component of asthma. There is evidence of neutrophil recruitment⁸ and increased chemotactic activity⁹ in experimental asthma, and neutrophil depletion ablates the late-phase response.^{10, 11}

Dapsone, a sulfone (4,4'-diaminodiphenyl sulfone) used in the treatment of leprosy and a variety of cutaneous and rheumatologic disorders, inhibits neutrophil function.¹² It decreases neutrophil production of reactive oxygen intermediates,^{13, 14} chemilumines-

Abbreviation used

PEFR: Peak expiratory flow rate

cence,^{13, 15, 16} chemotaxis,¹⁷ and injury to pulmonary epithelial cells.¹⁸

Because of the possible role of neutrophils in asthma, inhibitory effects of dapsone on neutrophils, and its therapeutic effects in a variety of inflammatory disorders, we studied the steroid-sparing effects of dapsone in 10 patients in a preliminary open trial.

MATERIAL AND METHODS

Patients

Ten patients, aged 23 to 80 years, with steroid-dependent asthma meeting American Thoracic Society Diagnostic criteria,¹⁹ completed this study after giving informed consent (Table I). Each patient required steroids despite an optimal regimen that included bronchodilators and inhaled steroids. Duration of continuous steroid therapy ranged from 1.3 to 30 years. All patients demonstrated steroid morbidity and had failed one or more attempts at steroid weaning within the previous 12 months. Mean daily steroid dose in prednisone equivalence ranged from 5 to 60 mg. All patients were clinically stable at the time of entry into the study.

Three patients did not complete the study and are not included in data analysis. One patient stopped dapsone at week 2 because of a vague feeling of malaise, one patient stopped at month 2 for rash and thrombocytopenia, and one patient stopped at month 7 because of a psychiatric disorder.

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TABLE I. Patient demographics

Patient	Age (yr)	Sex	IgE (IU/ml)	Prednisone treatment	
				Mean dose (mg/day)	Duration (yr)
J. B.	43	M	30	7.8	1.3
M. P.	55	F	10	16.4	24
S. C.	80	F	114	10	8
T. G.	30	F	129	10	2.7
C. G.	23	F	332	19.8	5.1
J. M.	51	M	82	7	2
R. S.	54	F	70	9.6	3
L. C.	54	F	20	5	6
M. M.	53	F	55	60	2.8
T. C.	57	M	5	15.4	30

Excluded were patients with concomitant severe medical illness, such as diabetes, cardiovascular, hepatic, or renal disease, history of poor compliance or severe psychiatric disorder, glucose-6-phosphate dehydrogenase deficiency, history of anemia or hemolysis, nonasthmatic pulmonary disease, abnormal diffusion capacity for carbon monoxide, reproductive or lactating female patients, and patients receiving concomitant treatment with rifampin or probenecid (which affect dapsone metabolism).

Study design

Before entry into the study, all patients were optimized on a therapeutic regimen including theophylline adjusted to therapeutic blood levels, inhaled β -agonists, and inhaled steroids. After a 4-week baseline period receiving their usual regimen, patients started receiving dapsone, 100 mg, twice daily, by mouth, and were followed for periods ranging from 7.4 to 20 months. Baseline studies included history and physical examination, spirometry, diffusion capacity for carbon monoxide, chest x-ray, sinus x-rays, glucose-6-phosphate dehydrogenase, complete blood count, urinalysis, IgE, theophylline level, chemistry panel, and thyroid panel. Patients kept daily records of medications, PEFR with a mini-PEFR meter, nebulization frequency, and symptom scores. The daily symptom score ranging from 0 to 15 consisted of a rating from 0 (no symptoms) to 1 (mild), 2 (moderate), and 3 (severe) for each of five parameters, including cough, wheeze, dyspnea, nocturnal awakening, and limitation of activity. After the baseline period and during the dapsone-treatment phase, patients were observed and examined weekly for the first 3 months and monthly thereafter. At each visit, pill counts were performed, and studies, including spirometry, theophylline level, and complete blood count were obtained. The patients were maintained with their prestudy therapeutic regimen, which included β -agonists and theophylline, but after stabilization with dapsone, inhaled steroids were stopped in all patients. Theophylline doses were adjusted as was necessary to maintain a therapeutic blood level. The oral steroid dose was tapered according to the physician's clinical assessment.

TABLE II. Group clinical parameters before and after dapsone therapy

Mean monthly	Dapsone		
	Before*	With†	Significance
Cumulative prednisone dosage (mg)	428.2	82.3	$p < 0.02$
Symptom scores	134.8	100.1	NS
Nebulizer usage frequency	283.7	271.8	NS
% Predicted home monitored PEFR	72.0	76.9	NS
% Predicted FEV ₁	83.4	78.4	NS

*Four-week baseline before starting dapsone.

†Latest 4-week period of dapsone therapy.

Data analysis

To minimize day-to-day variability, parameters, including steroid dose, number of bronchodilator nebulizations, and symptom scores, were evaluated during 4-week cumulative periods. Additional parameters included mean daily PEFR and spirometry at each clinic visit. Each patient's 4-week baseline data were compared to the latest available 4-week interval with Student's *t* test. A level of significance of 5% was considered meaningful.

RESULTS

Mean 4-week cumulative steroid dose was reduced from 428 mg to 82.3 mg ($p < 0.02$; Table II). Five of 10 patients stopped steroids by month 6 of dapsone, and two additional patients stopped by month 13. Two other patients followed for shorter periods demonstrated a coincidental 74% reduction in their steroid dose, and one patient clearly demonstrated no response. Despite reducing or stopping steroids in the nine responders, we did not observe any clinical wors-

TABLE III. Individual responses to dapsone therapy

Patient	Initial prednisone dose (mg/day)	Final prednisone dose (mg/day)	Time receiving dapsone (mo)	Time receiving dapsone to time steroids stopped (mo)	Subsequent steroid-free duration (mo)
J. B.	7.8	0	18.4	6	12.4
M. P.	16.4	0	18.9	5.3	13.6
S. C.	10	0	20	10.8	9.2
T. G.	10	0	18.3	13.3	5
C. G.	19.8	0	16.3	3.3	13*
J. M.	7	0	15.8	6.3	9.5*
R. S.	9.6	9.8	8.5	N/A	N/A
L. C.	5	0	7.4	5.3	2.1
M. M.	60	15.6	6.1	N/A	N/A
T. C.	15.4	4	3.5	N/A	N/A

N/A, Not applicable.

*Required one to three short courses of prednisone therapy.

ening as demonstrated by unchanged symptom scores, PEFR, nebulization frequency, and spirometry (Table II).

Clinically evident steroid reduction became apparent from month 3 to month 10 of dapsone treatment. The seven patients who stopped steroids have subsequently been maintained with dapsone for periods of 7.4 to 20 months and continued to do well (Table III). One responder has required three short courses of prednisone during a period of 9.5 months and one patient, a single course in 13 months of follow-up. None of the patients has required emergency care or hospitalization.

An unexpected finding was transiently elevated theophylline levels to a maximum of 33.4 $\mu\text{g/ml}$ at weeks 2 to 12 in four patients. These elevated levels were rapidly corrected to between 10 and 20 $\mu\text{g/ml}$. The most commonly observed adverse effect of dapsone was significant anemia in nine of 10 patients, with a mean hemoglobin drop of 3.6 gm/dl. In a few patients, dapsone dose was decreased to 50 mg, twice daily, because of anemia.

Three additional patients failed to complete the study, one because of malaise, one because of rash and thrombocytopenia, and one patient because of a psychotic episode (Table V).

DISCUSSION

This study demonstrated that nine of 10 steroid-dependent patients were able to substantially reduce or stop steroids while they were taking dapsone. Although designed in accordance with American Academy of Allergy and Immunology guidelines for pilot studies,²⁰ the limitations of an unblinded study in a small number of patients are obvious, and these findings must be interpreted with caution. If these preliminary findings are confirmed, however, dapsone

may have steroid-sparing effects, and the results may have implications regarding the role of neutrophils in asthma.

Although there is incomplete and conflicting evidence regarding the importance of neutrophils in human asthma, several studies suggest a possible role. The inflammatory process expends considerable chemotactic effort to recruit neutrophils to the site of hypersensitivity reactions via mediators, including platelet-activating factor,²¹ leukotriene B₄,^{22, 23} C5a,²⁴ and neutrophil chemotactic factor, which has been identified as interleukin-8. Neutrophil chemotactic factor, for example, is increased in immunologic and nonimmunologic asthma models, including antigen challenge,²⁵⁻²⁸ status asthmaticus,²⁹ aspirin-induced asthma,³⁰ nebulized distilled water-induced asthma,³¹ and toluene diisocyanate-induced asthma.³²

A number of studies suggest this chemotactic activity results in recruitment of neutrophils in asthma. Increased numbers of neutrophils are observed in the sputum of patients with asthma,³³ autopsies as a result of fatal asthma,³⁴ in toluene diisocyanate-induced asthma,^{35, 36} ozone-induced asthma,^{37, 38} and allergen bronchoprovocation.^{8, 39, 40} Furthermore, increased neutrophil numbers and activation are found in late-phase reactions.^{41, 42}

Further evidence for the importance of neutrophils in asthma is found in depletion studies. Neutrophil depletion by vinblastine,⁴³ antineutrophil antiserum,⁴⁴ hydroxyurea,¹⁰ and nitrogen mustard¹¹ abrogates the late-phase reaction and in some models decreases bronchial hyperreactivity.

Neutrophils mediate lung damage, in part, through their myeloperoxidase-H₂O₂-halide system.^{45, 46} Although the role of this system in asthma is unclear, basal production of superoxide by atopic neutrophils is greater than in control subjects.⁴⁷ In addition, su-

TABLE IV. Dapsone therapy in other diseases

Rheumatoid vasculitis
Cutaneous vasculitis
Subcorneal pustular dermatosis
Bullous pemphigoid
Systemic lupus erythematosus
Sweet's syndrome
Pustular psoriasis
Rheumatoid arthritis
Crohn's disease
Relapsing polychondritis
Pemphigus
Chronic urticaria (steroid-dependent)
Pyoderma gangrenosum
Oral lichen planus

peroxide generation by *N*-formyl-methionyl-leucyl-phenylalanine-stimulated neutrophils from subjects with asthma is increased^{47, 48} and parallels the degree of bronchial hyperreactivity.⁴⁸ Superoxide may also play an amplifying role in asthma by inducing additional mast cell degranulation.⁴⁹

Dapsone was chosen as a study drug because it has been demonstrated to affect neutrophil function, in part by inhibiting the lysosomal myeloperoxidase-H₂O₂-halide system.^{12, 50, 51} Studies of human neutrophils demonstrate that dapsone inhibits production of reactive oxygen intermediates,^{13, 14} decreases neutrophil chemiluminescence,^{13, 15, 16} decreases *N*-formyl-methionyl-leucyl-phenylalanine-induced neutrophil chemiluminescence¹⁶ and chemotaxis,¹⁷ inhibits pulmonary epithelial cell damage by neutrophils,¹⁸ and also inhibits mast cell prostaglandin D₂ release in rats.⁵³ In addition, dapsone has been studied in a variety of inflammatory disorders, many associated with histologic evidence of neutrophil infiltration⁵² or participation of mast cells (Table IV).⁵³ There is no current evidence, however, regarding the possible mechanism of action of dapsone in asthma. If these preliminary clinical effects are confirmed, additional study into the mechanism of action will be required.

Our study population was clinically stable at the time of entry into the study. The relatively high baseline spirometry of our patients indicated mild airway obstruction, and the possibility that their baseline prednisone dose was higher than necessary cannot be excluded. However, all patients had experienced significant exacerbations on attempted steroid reduction in the past. In contrast to prior efforts with these patients, there was no evidence of clinical deterioration with steroid reduction in this study.

Although dapsone can produce a variety of adverse reactions such as (1) neurologic reactions, including neuropathy and psychosis, (2) gastrointestinal reactions, including hepatitis, (3) hematologic reactions, in-

TABLE V. Encountered complications with dapsone therapy

Anemia	9
Rash and thrombocytopenia*	1
Elevated theophylline levels	4
Tachyarrhythmia	1
Malaise*	1
Psychosis*	1

*Withdrew from the study.

cluding methemoglobinemia, hemolysis, leukopenia, agranulocytosis, and (4) cutaneous reactions, it has a generally acceptable safety profile,⁵⁴ having been used to treat millions of patients since its introduction in the 1940s. The most common reaction is dose-dependent hemolytic anemia secondary to methemoglobinemia, with expected hemoglobin drops of 2 gm/dl. In this study, nine of 10 patients developed significant anemia, averaging hemoglobin drops of 3.6 gm/dl, probably caused by the relatively high dose of dapsone. However, there was no obvious clinical impact. One subject developed a tachyarrhythmia that responded to digitalization. The relationship of this occurrence to dapsone in this elderly individual is uncertain.

An unexpected finding was transient elevation of theophylline levels to as high as 33.4 µg/ml in four patients. This finding suggests either an effect of dapsone on theophylline clearance or better patient compliance. Although dapsone has never been reported to decrease theophylline clearance, this phenomenon cannot be excluded. Theophylline levels in the four patients demonstrating increases were rapidly corrected; therefore, it is unlikely any apparent therapeutic effect resulted from impaired theophylline clearance.

Three additional patients did not complete the study. One patient withdrew at week 2 because of a vague sense of malaise and weakness. Another patient was withdrawn because of rash and thrombocytopenia at month 2, and a third patient was withdrawn at month 7 because of onset of an acute psychosis, a complication reported with dapsone on rare occasions.⁵⁴ This individual had a history of psychologic problems in the past, and the relationship of this occurrence to dapsone is uncertain.

It is unlikely that any confounding variables affected our observations. Patients were enrolled in the study at different time periods, and any seasonal effect is unlikely. Since no concomitant medications were added to the regimen, any observed effects are presumed attributable to dapsone alone. In fact, aerosol steroids were stopped in all patients; therefore, the clinical stability with dapsone has persisted in the absence of steroid therapy.

In summary, because of the putative role of neu-

trophils in asthma and the late-phase reaction, and the known anti-inflammatory and neutrophil-inhibiting properties of dapsone, we hypothesized that dapsone may be effective in diminishing steroid requirements in severe asthma. Since preliminary findings in this open pilot study support the hypothesis, controlled clinical trials are warranted.

REFERENCES

- Barnes P. A new approach to the treatment of asthma. *N Engl J Med* 1989;321:1517-27.
- Muranaka M, Nakajima K, Suzuki S. Bronchial responsiveness to acetylcholine in patients with bronchial asthma after long-term treatment with gold salt. *J ALLERGY CLIN IMMUNOL* 1981;67:350-6.
- Bernstein D, Bernstein IL, Bodenheimer SS, Pietrusko RG. An open study of Auranofin in the treatment of steroid-dependent asthma. *J ALLERGY CLIN IMMUNOL* 1988;81:6-16.
- Yamauchi N, Suko M, Morita Y, Suzuki S, Ito K, Miyamoto T. Decreased airway responsiveness to histamine in gold salt-treated guinea pigs. *J ALLERGY CLIN IMMUNOL* 1984;74:802-7.
- Klaustermeyer W, Noritake D, Kwong F. Chrysotherapy in the treatment of corticosteroid-dependent asthma. *J ALLERGY CLIN IMMUNOL* 1987;79:720-5.
- Mullarkey M, Blumenstein B, Andrade W, Bailey G, Olason I, Wetzel C. Methotrexate in the treatment of corticosteroid-dependent asthma. *N Engl J Med* 1988;318:603-7.
- Charous B. Open study of hydroxychloroquine in the treatment of severe symptomatic or corticosteroid-dependent asthma. *Ann Allergy* 1990;65:53-8.
- Metzger W, Moseley P, Nugent K, Richerson H, Hunninghake G. Local antigen challenge and bronchoalveolar lavage of allergic asthmatic lungs. *Chest* 1985;87(Suppl):155-6.
- Carroll M, Durham S, Walsh G, Kay A. Activation of neutrophils and monocytes after allergen and histamine-induced bronchoconstriction. *J ALLERGY CLIN IMMUNOL* 1985;75:290-6.
- O'Byrne P, Waters E, Gold B, et al. Neutrophil depletion inhibits airway hyperresponsiveness induced by ozone exposure. *Am Rev Respir Dis* 1984;130:214-9.
- Murphy K, Wilson M, Irvine C, et al. The requirement for polymorphonuclear leukocytes in the late asthmatic response and heightened airways reactivity in an animal model. *Am Rev Respir Dis* 1986;134:62-8.
- Stendahl O, Molin L, Dahlgren C. The inhibition of polymorphonuclear leukocyte cytotoxicity by dapsone. *J Clin Invest* 1970;62:214-20.
- Niwa Y, Sakane T, Miyachi Y. Dissociation of the inhibitory effect of dapsone on the generation of oxygen intermediates—in comparison with that of colchicine and various scavengers. *Biochem Pharmacol* 1984;33:2355-60.
- Miyachi Y, Niwa Y. Effects of potassium iodide, colchicine, and dapsone on the generation of polymorphonuclear leukocyte-derived oxygen intermediates. *Br J Dermatol* 1982;107:209-14.
- Webster G, Alexander J, MacArthur W, Leyden J. Inhibition of chemiluminescence in human neutrophils by dapsone. *Br J Dermatol* 1984;110:657-63.
- Anderson R, Gatner E, van Rensburg C, Grabow G, Imcamp F. In vitro and in vivo effects of dapsone on neutrophil and lymphocyte functions in normal individuals and patients with lepromatous leprosy. *Antimicrob Agents Chemother* 1981;19:495-503.
- Harvath L, Yancey K, Katz S. Selective inhibition of human neutrophil chemotaxis to *N*-formyl-methionyl-leucyl-phenylalanine by sulfones. *J Immunol* 1986;137:1305-11.
- Martin W, Kachel D. Reduction of neutrophil-mediated injury to pulmonary endothelial cells by dapsone. *Am Rev Respir Dis* 1985;131:544-7.
- ATS Scientific Assembly on Clinical Problems. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. *Am Rev Respir Dis* 1987;136:225-44.
- Nicklas RA, Sheffer AL, Adkinson NF Jr. Report of the AAAI task force on guidelines for clinical investigation of nonbronchodilator antiasthmatic drugs: study design [Workshop]. *J ALLERGY CLIN IMMUNOL* 1986;78:507-17.
- Czarnetzki M, Benveniste J. Effect of 1-0-octadecyl-2-0-acetyl-SN-glycero-3-phosphorylcholine (PAF-acether) on leukocytes. I. Analysis of the in vitro migration of human neutrophils. *Chem Phys Lipids* 1981;29:317-26.
- Silbaugh S, Stengel P, Williams G, Herron D, Gallagher P, Baker S. Effects of leukotriene B₄ inhalation: airway sensitization and lung granulocyte infiltration in a guinea pig. *Am Rev Respir Dis* 1987;136:930-4.
- Freeland H, Pipkorn U, Schleimer R, et al. Leukotriene B₄ as a mediator of early and late reactions to antigen in humans: the effect of systemic glucocorticoid treatment in vivo. *J ALLERGY CLIN IMMUNOL* 1989;83:634-42.
- Irvin C, Berend N, Henson P. Airways hyperreactivity and inflammation produced by aerosolization of human C5a des arg. *Am Rev Respir Dis* 1986;134:777-83.
- Atkins P, Norman M, Weiner H, Zweiman B. Release of neutrophil chemotactic activity during immediate hypersensitivity reactions in humans. *Ann Intern Med* 1977;86:415-8.
- Nagy L, Lee T, Kay A. Neutrophil chemotactic activity in antigen-induced late asthmatic reactions. *N Engl J Med* 1982;306:497-501.
- Papageorgiou N, Lee TH, Nagakura T, Cromwell O, Wraith D, Kay AB. Neutrophil chemotactic activity in milk-induced asthma. *J ALLERGY CLIN IMMUNOL* 1983;72:75-82.
- Durham S, Lee TH, Cromwell O, et al. Immunologic studies in allergen-induced late-phase asthmatic reactions. *J ALLERGY CLIN IMMUNOL* 1984;74:49-60.
- Buchanan D, Cromwell O, Kay A. Neutrophil chemotactic activity in acute severe asthma (status asthmaticus). *Am Rev Respir Dis* 1987;136:1397-1402.
- Hollingsworth H, Downing E, Braman S, Glassroth J, Binder R, Center D. Identification and characterization of neutrophil chemotactic activity in aspirin-induced asthma. *Am Rev Respir Dis* 1984;130:373-9.
- Shaw R, Anderson S, Durham S, et al. Mediators of hypersensitivity in "fog"-induced asthma. *Allergy* 1985;40:48-57.
- Sastre J, Banks DE, Lopez M, Barkman HW, Salvaggio JE. Neutrophil chemotactic activity in toluene diisocyanate (TDI)-induced asthma. *J ALLERGY CLIN IMMUNOL* 1990;85:567-72.
- Sanerkin N, Evans D. The sputum in bronchial asthma: pathognomonic patterns. *J Pathol Bact* 1965;89:535-41.
- Dunnill N, Mossarella G, Anderson J. A comparison of the quantitative anatomy of the bronchi in normal subjects and status asthmaticus, in chronic bronchitis, and in emphysema. *Thorax* 1969;24:176.
- Gordon T, Sheppard D, McDonald D, Distefano S, Scypinski L. Airway hyperresponsiveness and inflammation induced by toluene diisocyanate in guinea pigs. *Am Rev Respir Dis* 1985;132:1106-12.
- Fabbri L, Boschetto P, Zocca E, et al. Bronchoalveolar neutrophilia during late asthmatic reactions induced by toluene diisocyanate. *Am Rev Respir Dis* 1987;136:32-42.
- Holtzman M, Fabbri L, O'Byrne P, et al. Importance of airway

- inflammation for hyperresponsiveness induced by ozone. *Am Rev Respir Dis* 1983;127:686-90.
38. Fabbri L, Aizawa H, Alpert S, et al. Airway hyperresponsiveness and changes in cell counts in bronchoalveolar lavage after ozone exposure in dogs. *Am Rev Respir Dis* 1984;129:288-91.
 39. Hutson P, Church M, Clay T, Miller P, Holgate S. Early and late-phase bronchoconstriction after allergen challenge of non-anesthetized guinea pigs. I. The association of disordered airway physiology to leukocyte infiltration. *Am Rev Respir Dis* 1988;137:548-57.
 40. Iijima H, Ishii M, Yamauchi K, et al. Bronchoalveolar lavage and histologic characterization of late asthmatic response in guinea pigs. *Am Rev Respir Dis* 1987;136:922-9.
 41. Durham S, Carroll M, Walsh G, Kay A. Leukocyte activation in allergen-induced late-phase asthmatic reactions. *N Engl J Med* 1984;311:1398-1402.
 42. Marsh W, Irvin C, Murphy K, Behrens B, Larsen G. Increases in airway reactivity to histamine and inflammatory cells in bronchoalveolar lavage after the late asthmatic response in an animal model. *Am Rev Respir Dis* 1985;131:875-9.
 43. Lemanske R, Guthman D, Orgel H, Barr L, Kaliner M. The biological activity of mast cell granules. VI. The effect of vinblastine-induced neutropenia on rat cutaneous late-phase reactions. *J Immunol* 1983;130:2837-42.
 44. Lemanske R, Guthman D, Kaliner M. The biologic activity of mast cell granules. VII. The effect of anti-neutrophil antibody-induced neutropenia on rat cutaneous late-phase reactions. *J Immunol* 1983;131:929-33.
 45. Shasby D, Vanbentheysen K, Tate R, Shasby S, McMurtry I, Repine J. Granulocytes mediate acute edematous lung injury in rabbit and in isolated rabbit lungs perfused with phorbol myristate acetate: role of oxygen radicals. *Am Rev Respir Dis* 1982;125:443-7.
 46. Petrone W, English D, Wong K, McCord J. Free radicals and inflammation: superoxide-dependent activation of a neutrophil chemotactic factor in plasma. *Proc Natl Acad Sci USA* 1980;77:1159-63.
 47. Styrt B, Rocklin RE, Klempner MS. Characterization of the neutrophil respiratory burst in atopy. *J ALLERGY CLIN IMMUNOL* 1988;81:20-6.
 48. Meltzer S, Goldberg B, Lad P, Easton J. Superoxide generation and its modulation by adenosine in the neutrophils of subjects with asthma. *J ALLERGY CLIN IMMUNOL* 1989;83:960-6.
 49. Henderson W, Chi E, Klebanoff S. Eosinophil peroxidase-induced mast cell secretion. *J Exp Med* 1980;152:265-79.
 50. Kazmierowski J, Ros J, Peizner D, Wuepper K. Dermatitis herpetiformis: effects of sulfones and sulfonamides on neutrophil myeloperoxidase-mediated iodination and cytotoxicity. *J Clin Immunol* 1984;4:55-64.
 51. Theron A, Anderson R. Investigation of the protective effects of the antioxidants ascorbate, cysteine and dapsone, on the phagocyte-mediated oxidative inactivation of human alpha-one protease inhibitor in vitro. *Am Rev Respir Dis* 1985;132:1049-54.
 52. McDougall A. Dapsone. *Clin Exp Dermatol* 1979;4:139-41.
 53. Ruzicka T, Wasserman SI, Soter NA, Printz MP. Inhibition of rat mast cell arachidonic acid cyclooxygenase by dapsone. *J ALLERGY CLIN IMMUNOL* 1983;72:365-70.
 54. Graham W. Adverse effects of dapsone. *Int J Dermatol* 1975;14:494-500.

Synthesis of platelet-activating factor by human monocytes stimulated by platelet-activating factor

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The capacity of platelet-activating factor (PAF) to stimulate its own synthesis by human monocytes was examined. Adherent human monocytes of >85% purity were incubated with 100 fM to 10 nM of PAF in the presence of 20 µCi of [³H]acetic acid to radiolabel newly synthesized PAF. After incubation for 15 minutes to 15 hours, PAF was purified by high-performance liquid chromatography, and newly synthesized PAF was quantified by its radioactivity. PAF stimulated its own synthesis in a dose-related manner with a maximal twofold to threefold increase in synthesis at 10 pM to 100 pM of PAF. Maximal PAF synthesis occurred after incubation for 6 to 8 hours. There was a good correlation (r = 0.95) between PAF quantified by [³H]acetic acid incorporation and by rabbit platelet aggregation bioassay, indicating that the radioactive material is PAF. The protein synthesis inhibitor, cycloheximide, did not inhibit delayed PAF synthesis, indicating that delayed PAF synthesis does not require protein synthesis. PAF is metabolized rapidly in vivo. The capacity of PAF to stimulate its own synthesis would result in a prolonged effective half-life in vivo. This prolonged half-life could contribute to the capacity of PAF to induce prolonged inflammatory reactions in vivo. (J ALLERGY CLIN IMMUNOL 1991;87:715-20.)

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