Comparison of the effects of two cytotoxic drugs and of antilymphocytic serum

On immune and non-immune inflammation in experimental animals

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This paper is concerned with the suppressive effects in rats and guinea-pigs of two cytotoxic agents in current clinical use and of antilymphocytic serum on inflammation of immune origin and on inflammation caused in other ways. Such a study appeared to us to be needed, since with the increasing use of powerful antimetabolites in the treatment of patients with putative autoimmune disorders, such as the connective tissue diseases, effects ascribed to interference with processes of immunity might be due to an anti-inflammatory action. We have studied similar parameters to assess the effects of antilymphocytic serum on immune and non-immune inflammation.

Methods

Animals were outbred Wistar rats, more than 3 months old, and guinea-pigs weighing 350-500 g.

AZATHIOPRINE (Imuran, B.D.H.) was dissolved in alkaline saline and injected intramuscularly. Control animals were injected with an equal volume of alkaline saline.

CYCLOPHOSPHAMIDE (Endoxana, Ward Blenkinsop) was given by the intraperitoneal route and an equal volume of saline to control animals.

ANTITHYMOCYTE SERUM was produced from rabbits which received one injection of 10^9 rat thymocytes with complete Freund's adjuvant intracutaneously, followed by two subcutaneous doses of thymocytes in saline at weekly intervals. Serum was heated at 56°C . for 30 min. absorbed with packed rat erythrocytes, filtered and stored frozen.

Rats or guinea-pigs were immunized by intracutaneous injection of 100 or 500 μg . bovine γ -globulin (BGG) respectively, emulsified with Freund's complete adjuvant or in other cases with Freund's adjuvant emulsified with saline only. Guinea-pigs were tested by intracutaneous injection in the shaved skin of the back with 1 μg . BGG or 1 μg . tuberculin purified protein derivative (PPD) Diameters and skin-fold thickness of reactions were measured

at 24 hrs. Rats were tested by injection of 25 μg . PPD in the skin of an ear. Thickness was measured before and 24 hrs after injection with a spring-loaded micrometer.

Arthritis was produced in similarly immunized guinea-pigs by intra-articular injection of 500 μg . sterile BGG in one knee, and a similar amount of PPD in the other. For histological study, synovium was dissected free from the patellar tendon, fixed in 10 per cent. formaldehyde, sectioned, and stained with haematoxylin and eosin.

Skin windows were applied to the shaved abdominal skin of rats as described by Volkman and Gowans (1965). This technique allows the collection of an inflammatory cell population, whose composition is governed by the duration of application of the cover slip to the skin. A small drop of 1/200 Old Tuberculin was applied to the skin site as an irritant. The cover slips were removed after 24 hrs and stained with Leishman's stain. Since the distribution of cells on the cover slips was quite irregular, only an impression of numbers could be formed and this was classified + to +++. Only gross differences between exudates could therefore be accepted as drug effects.

Polyvinyl alcohol sponges (Prosthesis, Ramer Chemical Co.) each 1 cm.² approx., were implanted subcutaneously in rats. They were taken out at varying intervals after injection. Loosely adhering tissue was removed. A small piece was fixed and sectioned for histology. The remaining sponge, containing tissue, was weighed, minced with scissors, washed in saline, followed by absolute ethanol, and then extracted with cold perchloric acid, following the Schmitt-Thannhauser-Schneider procedure for RNA and DNA (as given by Volkin and Cohn, 1954). DNA content was read at a wavelength of 267 m μ . Finally the solution was brought to an alkaline pH by addition of 40 per cent. NaOH, and added to Bray's scintillation counting medium. Radioactivity was assayed in a Tracerlab Scintillation counter.

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Results

A. EFFECT OF AZATHIOPRINE

(1) Skin windows in rats

Six animals, weighing between 300 and 400 g. were given 15 mg. azathioprine/kg./day for 10 days. A skin window was applied on the day before treatment began and another on the 9th day of treatment. Each of these was removed 24 hrs after application (Fig. 1). The amount of cellular exudate (Fig. 2) on the cover glasses is expressed arbitrarily as 0 to +++, indicating a range of no identifiable cells to confluent cell sheets covering a considerable part of the cover glass. In three animals there was a decrease, in two no change, and in one an increase in cellularity.

In a second experiment, six rats were given 15 mg. azathioprine/kg./day, and six others acted as controls, injected with 0.1N NaOH used for dissolving azathioprine. In each animal only one skin window was applied, at the end of the treatment period. As shown in Fig. 2 fewer cells were seen on skin windows of treated than of control rats, although, as in the previous experiment, the effect was not dramatic.

Another group of eight rats was therefore given 30 mg. azathioprine/kg./day for 10 days, and a skin window applied on the last day of treatment. Fig. 2 shows that skin windows from five animals showed no cells, while three showed only a very small number of cells expressed as +.

We concluded from this series of experiments that azathioprine given in adequate dosage was capable of suppressing the inflammatory response, as tested by the skin window technique.

FIG. 2 Concentration of mononuclear exudate cells on coverslips in untreated rats, controls treated with NaOH injections, and groups injected with 15 or 30 mg. azathioprine/kg./day.

(2) Effect on other inflammatory reactions in rats

Delayed hypersensitivity to PPD was assessed by the swelling in Wistar rats' ears which had been immunized by injection of Freund's complete adjuvant, and 2 weeks later given 11 days' treatment of 30 mg. azathioprine/kg./day. On the 19th day of treatment, 25 µg. PPD were injected into one ear. Readings taken at 24 hrs varied from 28 to 100 per cent. thickness increase (average 69 per cent.). Untreated control rats varied from 52 to 73 per cent. (average 61 per cent.). It is evident that the PPD reaction was not suppressed by this treatment in rats.

FIG. 1 Mononuclear cells on a 24-hr skin window in a normal rat. Leishman's stain. $\times 300$.

Six Wistar rats were immunized with complete Freund's adjuvant and 2 weeks later treatment with 50 mg. azathioprine/kg./day was started. On the 10th day 500 µg. sterile PPD were injected into one knee joint, and synovium was removed when the animals were killed 48 hrs later. Six control rats were not given azathioprine, but were treated identically otherwise. The degree of inflammation (which was assessed histologically) was not significantly different in the two groups of animals.

It appears that, although azathioprine had a definite suppressive effect on cell exudation on skin windows, no such effect could be demonstrated on delayed hypersensitivity responses to PPD in rats. A further group of three rats was given 50 mg. azathioprine/kg./day, with another group of three acting as NaOH-injected controls. On the second day of the experiment, two pieces of polyvinyl sponge were inserted in the subcutaneous plane of the back in each rat. Treatment was continued until the sponges were removed 9 days later. The difference between the control sponges showing infiltration by granulation tissue, and the poorly infiltrated sponges from azathioprine-treated animals was striking.

Most of the experimental animals, whether given azathioprine or NaOH control injections, showed some loss of weight, but only those receiving 50 mg./kg./day showed a significant drop of WBC counts. In this latter group the average drop was of approximately 50 per cent.

(3) *Effect on inflammatory reactions of guinea-pigs*

Eight guinea-pigs were injected with 30 mg. azathioprine per day for 15 days, while seven other guinea-pigs were injected with NaOH as controls. All had been immunized by an injection of 1 mg. bovine gamma-globulin in complete Freund's adjuvant 2 weeks before azathioprine or NaOH injections were begun. On the 15th day of this treatment the animals were tested by intracutaneous injections of 1 µg. BGG and 1 µg. PPD, and the reactions were read 24 hrs later. The results are shown in Table I. It is

Table I *Effect of azathioprine on 24-hr skin reactions in guinea-pigs*

No. in group	Treatment	1 µg. BGG	1 µg. PPD
7	Alkaline saline control	10.9 (9-14), 60 per cent.	15.7 (14-20), 81 per cent.
8	6-mercapto-purine	7.1 (5-10), 26 per cent.	11.4 (8-14), 39 per cent.

Results are averages of reactions measured in mm. with range in parenthesis; skin thickness increase expressed as percentage increase over normal skin (for both antigens $P = < 0.01$).

evident that azathioprine treatment was associated with depressed 24-hr specific skin reactions.

Four guinea-pigs similarly immunized and treated with NaOH, and four others with azathioprine for 15 days, were injected with 500 µg. BGG in the right knee joint and 500 µg. PPD in the left, following a procedure used in earlier experiments (Loewi, 1968). Histologically, 48 hrs after such challenge no differences could be established in the severity of synovitis in the two groups.

B. EFFECT OF CYCLOPHOSPHAMIDE

(1) *Delayed hypersensitivity reactions*

A group of eleven adult Wistar rats was immunized with Freund's complete adjuvant, and 2 weeks later tested by injection of 25 µg. PPD into one ear. Reactions at 24 hrs showed thickness increases varying between 67 and 108 per cent. (average 84 per cent.). Six rats received 20 mg. cyclophosphamide/kg./day by intraperitoneal injection, the remaining five rats being given saline injections as controls; 9 days later the rats' contralateral ears were tested by PPD injection. Whereas the treated animals had reactions of 14 to 41 per cent. (average 28 per cent.), the controls varied from 82 to 118 per cent. (average 104 per cent.) ($P = < 0.01$).

Guinea-pigs immunized with BGG and complete Freund's adjuvant were similarly tested after 9 days' treatment by intraperitoneal injection of 20 mg. cyclophosphamide/kg./day. The results are shown in Table II. A depression of responses is shown, although this was not as striking as in the rats.

Table II *Effect of cyclophosphamide on 24-hr skin reactions in guinea-pigs*

No. in group	Treatment	1 µg. BGG	1 µg. PPD
9	Cyclophosphamide	9.1 (6-12), 14 per cent.	12.8 (12-14), 27 per cent.
4	Saline	15.0 (14-16), 38 per cent.	18.8 (18-20), 54 per cent.

Results are averages of skin reaction measured in mm., range in parentheses; skin thickness increase is expressed as percentage increase over normal skin.

(2) *Experimental arthritis*

Guinea-pigs were immunized with BGG and complete Freund's adjuvant, and 2 weeks later were given 20 mg. cyclophosphamide/kg./day, while controls received saline injections. On the 10th day treatment was stopped and each animal received

FIG. 3 Synovial membrane of a guinea-pig which had received intra-articular BGG and treatment with 20 mg. cyclophosphamide/kg./day. Low-grade inflammation is shown. Haematoxylin and eosin. $\times 300$.

FIG. 4 Synovial membrane of a guinea-pig which had received saline injections as a control for cyclophosphamide. Extensive inflammatory exudate. Haematoxylin and eosin. $\times 300$.

challenge injections of 500 μ g. BGG in the right knee and 500 μ g. PPD in the left. The synovia from three treated animals and one control were examined after 48 hrs; two of the treated animals showed only slight inflammatory changes while one treated and the one control showed the severe inflammatory reaction normally found. Other treated and control animals killed 4 days later or 10 days after the antigen injection into the knee joints showed the usual severe inflammatory changes (Loewi, 1968).

The effect of treatment on a pre-existing synovitis was examined in another group of twelve guinea-pigs immunized with BGG and adjuvant. All received injections of antigen into the knee joints.

Three animals received cyclophosphamide and three were given saline for 8 days, beginning on the day of joint challenge. Synovia from the three treated animals showed considerably less inflammatory infiltrate than those from the three controls (Figs 3 and 4).

In another six animals treatment with cyclophosphamide or saline was begun 3 days after joint chal-

lenge and was continued for 6 days. No difference was found in the gross or histological appearances of synovia from these animals. It was concluded that, although cyclophosphamide might have some effect on the early development of immune inflammation in the synovium, it had little or no influence when given after the inflammatory lesion had developed.

(3) *Sponge implants*

To test the effect on non-immune inflammation, polyvinyl sponge was implanted in the subcutaneous plane of the back of rats. This method was chosen so that the amount of granulation tissue formed might be measured. In order to obtain granulomata of different ages, sponges were inserted at different intervals after starting cyclophosphamide or saline injections. Each group consisted of three rats. Injections were given intraperitoneally (20 mg. cyclophosphamide/kg./day) for 10 days, and 3 hours before the sponges were removed one rat in each group of three was given 0.5 μ C. tritiated thymidine/g. body weight intravenously.

Histologically, sponges of 9 or 6 days' duration showed extensive granuloma in controls but very little cellular tissue with cyclophosphamide injections (Fig. 5, and Fig. 6, opposite). In autoradiographs up to 15 per cent. of cells were labelled in controls, while only a very occasional labelled cell was seen in the treated animals. Sponges which had been implanted 3 days before the end of an experiment showed only polymorphonuclear cells in both cyclophosphamide-treated and control animals. The results are shown in Table III. Total DNA was reduced as a result of cyclophosphamide treatment and the incorporation of tritiated thymidine into the cells of the granuloma after flash-labelling was also reduced. This suggests that the local cell proliferation of granuloma is reduced when cyclophosphamide is given. There may also be a reduction of normal invasion by inflammatory cells. It appears that cyclophosphamide, quite apart from the known effect on the process of immunization, may interfere with the evolution of the processes of inflammation.

C. EFFECT OF ANTITHYMOCYTE SERUM

Three rats received 1 ml. antithymocyte serum on each of two successive days by intraperitoneal injection. Three other rats received normal rabbit serum. Skin window cover slips were applied on the second day. No difference was seen in the extent or composition of cellular exudates between the two groups. Two other groups, each consisting of three rats, were treated similarly but tested by injection of 12.5 µg poly-L-lysine in one ear and 125 µg. in the other.

Table III *Effect of cyclophosphamide on sponge implant organization in rats*

<i>Treatment</i>	<i>Age of Animal implant No. (days)</i>	<i>µg. DNA/ 100 mg. sponge</i>	<i>c.p.m./µg. DNA</i>
Cyclophos- phamide I.P.	9	1 47 2 37 3 55	— — 11.3
	6	4 41 5 34 6 38	— — 5.8
	3	7 61 8 45 9 64	— — 2.1
	9	10 140 11 77 12 97	— — 22.4
	6	13 60 14 123 15 115	— — 21.8
	3	16 56 17 85 18 96	— — 1.4
Saline I.P.			

Swelling, measured 24 hrs later, was of similar extent in normal serum and antiserum-treated animals. Delayed hypersensitivity to PPD was assessed in six rats treated with intraperitoneal doses of 1 ml. antithymocyte serum and in six other rats treated with normal rabbit serum. The treated group showed

FIG. 5 *9-day sponge implant in a rat treated with 20 mg. cyclophosphamide/kg./day. Exudate contains very few cells. Haematoxylin and eosin. × 300.*

FIG. 6 9-day sponge implant in a control saline-injected rat. Cellular granuloma in sponge interstices. Haematoxylin and eosin. $\times 300$.

ear swelling of average value 44 per cent. (range 20 to 96 per cent.), the control group showed 84 per cent. (range 61 to 100 per cent.) ($P < 0.02 > 0.01$).

The effect of antiserum treatment on granuloma formation in response to a sponge implant was examined in three rats receiving 1 ml. antithymocyte serum by intraperitoneal injection on alternate days, another three rats injected with normal rabbit serum acting as controls. The sponges were removed on the 9th day after implantation and examined histologically. No differences could be detected in the amounts of granulation tissue formed in the two groups. Determination of the amounts of DNA similarly showed no significant difference.

It is apparent that, of the inflammatory reactions tested, only the delayed hypersensitivity reaction, and this only partially, showed suppression with antithymocyte serum treatment.

Discussion

The results show that both azathioprine and cyclophosphamide diminish the inflammatory response in guinea-pigs and in rats, but that the extent of this effect may differ in the two species. Furthermore, inflammation due to different stimuli was suppressed to varying extents. Thus, even large doses of azathioprine failed to affect delayed hypersensitivity reactions in rats, but diminished such reactions in guinea-pigs. On the other hand, this drug markedly affected chronic inflammatory invasion of sponge implants and cell exudation on skin windows in rats.

Cyclophosphamide administration reduced delayed hypersensitivity skin reactions in rats and guinea-pigs, and diminished sponge granuloma formation. Experimental arthritis was not apparently affected by azathioprine but was somewhat suppressed by cyclophosphamide.

The administration of antithymocyte serum showed a much greater selectivity in that no effect was seen on the cellular exudation on skin windows or in sponge implants, or as a result of the cutaneous injection of a nonspecific irritant such as polylysine, while the delayed hypersensitivity response to PPD in rats was diminished. This is in agreement with the findings of Waksman, Arbouys, and Arnason (1961), who showed a specific effect on cellular immune reactions. More recent work by Turk, Willoughby, and Stevens (1968) similarly showed no effect of antilymphocytic sera on chronic inflammation, while an effect on acute non-specific inflammation was ascribed to lowering of complement levels (Willoughby, Coote, and Turk, 1969).

The anti-inflammatory action of 6-mercaptopurine, a purine antagonist related to azathioprine, has been examined by Page, Condie, and Good (1962 a, b). They were able to suppress the non-specific response to subcutaneous ovalbumin injection in rabbits and the appearance of mononuclear cells on skin windows. Borel and Schwartz (1964) suppressed the Arthus reaction in rabbits with high antibody levels by 6-mercaptopurine administration. This was attributed to anti-inflammatory action. Arthus reactions could be elicited one week after cessation of drug administration.

In our experiments using azathioprine and cyclophosphamide, we found no evidence to support the conclusion drawn by Schwartz (1965), working with 6-mercaptopurine, that the mononuclear cells involved in an immunologically specific process were more susceptible to drug suppression than those involved in nonspecific inflammation. In azathioprine-treated rats we found suppression of some non-specific inflammatory reactions, while delayed hypersensitivity responses appeared to be intact.

Summary

Two cytotoxic drugs, azathioprine and cyclophosphamide, and antithymocyte serum were compared for their effects on immunologically-induced and on nonspecific inflammation in rats and guinea-pigs.

Azathioprine in rats suppressed the exudation of mononuclear cells on skin windows and the formation of granuloma in response to sponge implants.

There was no effect on delayed hypersensitivity responses to PPD or on PPD-induced synovitis in immunized animals. In guinea-pigs delayed hypersensitivity to BGG and PPD was significantly diminished by azathioprine.

Cyclophosphamide caused marked reduction of delayed hypersensitivity reactions in guinea-pigs and rats, and also partially suppressed immune synovitis when given before, or at the time of, antigen injection into the knee joints. The effect of cyclophosphamide on sponge implant granuloma formation was assessed quantitatively as well as histologically. Both total quantity of DNA and tritium incorporation after flash-labelling with tritiated thymidine were reduced.

Treatment with antithymocyte serum caused a partial suppression of delayed hypersensitivity to PPD in rats, while not affecting nonspecific inflammatory responses.

We thank Mr. A. P. P. Nind for DNA estimations, and Miss A. Temple for assistance.

References

- BOREL, Y., AND SCHWARTZ, R. (1964) *J. Immunol.*, **92**, 754 (Inhibition of immediate and delayed hypersensitivity in the rabbit by 6-mercaptopurine).
 LOEWI, G. (1968) *Immunology*, **15**, 417 (Experimental immune inflammation in the synovial membrane. I. The immunological mechanism).
 PAGE, A. R., CONDIE, R. M., AND GOOD, R. A. (1962a) *Amer. J. Path.*, **40**, 519 (Effect of 6-mercaptopurine on inflammation).
 —, —, — (1962b) *Blood*, **20**, 118 (Clinical studies on the anti-inflammatory activity of 6-mercaptopurine).
 SCHWARTZ, R. S. (1965) *Progr. Allergy*, **9**, 246 (Immunosuppressive drugs).
 TURK, J. L., WILLOUGHBY, D. A., AND STEVENS, J. E. (1968) *Immunology*, **14**, 683 (An analysis of the effects of some types of anti-lymphocyte sera on contact hypersensitivity and certain models of inflammation).
 VOLKIN, E., AND COHN, W. E. (1954) 'Estimation of nucleic acids', in 'Methods of Biochemical Analysis', vol. 1, p. 287. Interscience, New York.
 VOLKMAN, A., AND GOWANS, J. L. (1965) *Brit. J. exp. Path.*, **46**, 50 (The production of macrophages in the rat).
 WAKSMAN, B. H., ARBOUYS, S., AND ARNASON, B. G. (1961) *J. exp. Med.*, **114**, 997 (The use of specific 'lymphocyte' antisera to inhibit hypersensitive reactions of the 'delayed' type).
 WILLOUGHBY, D. A., COOTE, E., AND TURK, J. L. (1969) *J. Path. Bact.*, **97**, 295 (Complement in acute inflammation).

RÉSUMÉ

La comparaison entre les effets de deux médicaments cytotoxiques et ceux du sérum antilymphocytaire sur l'inflammation immune et non-immune chez les animaux de laboratoire

Deux médicaments cytotoxiques, azathioprine et cyclophosphamide, et le sérum antithymocytaire ont été comparés quant à leurs effets sur l'inflammation non-spécifique et celle immuno-induite chez les rats et les cobayes.

L'azathioprine chez les rats supprimait l'exudation des cellules mononucléaires aux 'fenêtres' de la peau et la formation de granulomes après les implantations d'éponge. Il n'y avait aucun effet sur l'hypersensibilité à retard due à la synovite causée par une protéine dérivée de la tuberculine purifiée (PPD) ou induite par

SUMARIO

Comparación de los efectos de dos drogas citotóxicas y del suero antilinfocítico en la inflamación immune y no immune en animales de laboratorio

Dos drogas citotóxicas, azatioprina y ciclofosfamida, fueron comparadas con suero antitimocítico para averiguar sus efectos en la inflamación inmunológicamente inducida y en la inflamación no específica, en ratas y cobayos.

En las ratas, la azatioprina suprimió la exudación de células mononucleares en ventanas epidérmicas y la formación de granuloma como reacción a las implantaciones de esponja. No tuvo ningún efecto en las reacciones de hipersensibilidad retardada a la proteína derivada de tuberculina purificada (PPD) o en la sinovitis inducida por PPD en animales inmunizados. En cobayos, la

cette protéine chez les animaux immunisés. Chez les cobayes l'hypersensibilité à retard à la gamma globuline bovine et à la PPD était diminuée d'une façon significative par l'azathioprine.

La cyclophosphamide causait une réduction marquée des réactions hypersensibles à retard chez les cobayes et les rats, et supprimait aussi en partie la synovite immune quand ce médicament était donné avant, ou au moment de l'injection d'antigène dans les articulations du genou. L'effet de la cyclophosphamide sur les granulomes par implantations d'éponge a été évalué quantitativement et histologiquement. La quantité totale de ADN ainsi que l'incorporation de tritium après 'flash-labelling' avec de la thymidine tritiée était réduite.

Le traitement avec du sérum antithymocytaire causait une suppression partielle de l'hypersensibilité à retard à la PPD chez les rats tandis que les réactions inflammatoires non-spécifiques n'étaient pas affectées.

hipersensibilidad retardada a la globulina gamma bovina y a la PPD fue disminuida considerablemente por la azatioprina.

La ciclofosfamida causó notable reducción de las reacciones de hipersensibilidad retardada en cobayos y ratas, y también suprimió parcialmente la sinovitis inmune cuando se administró antes o al tiempo de una inyección de antígeno en las articulaciones de la rodilla. El efecto de la ciclofosfamida en granulomas de implantación de esponja fue calculado tanto cuantitativa como histológicamente. Las cantidades totales de ADN y de incorporación de tritio después de 'flash-labelling' con tiamidina tritiada fueron reducidas. El tratamiento con suero antitimocítico causó una parcial supresión de la hipersensibilidad retardada al PPD en ratas sin afectar las reacciones inflamatorias no específicas.

and W. I. Glass outlined experiences with schemes already operating in New Zealand.

A further series of papers dealt with the place of physical medicine in the treatment of locomotor problems. Dr D. Gordon outlined the extent of the problem, Dr J. W. Gibb gave an account of a series of cases of painful necks classifying them from the clinical, prognostic, and therapeutic aspects, Dr M. J. Bishop pointed out the common ground in various theories of the aetiology of cervical headache, and Dr K. R. Orr talked on low back pain, emphasizing the frequency of various sacroiliac syndromes. Dr M. I. Hepburn discussed the importance of short leg in the production of back symptoms. Dr I. S. Broadfoot reviewed the cult of chiropractic with a plea that the medical profession should take positive action to counter the effects of expert sales talk. Dr R. G. Howes spoke on ice therapy in the treatment of various joint disorders. Dr D. Gash pointed out the economies which follow the establishment of industrial health clinics, particularly as applied to work accidents.

In February, 1970, the Association met in Dunedin with other specialist societies and the combined New Zealand and Australian sections of the College of Physicians. Dr John Webb, President of the Australian Rheumatism Association, spoke provocatively and very much to the point on politics and policies relating both individually and collectively to those interested in rheumatology—a theme also followed by Prof. T. C. Highton in his Presidential Address.

Professor Verna Wright

Dr Verna Wright has been appointed to a Personal Chair in Rheumatology, tenable at Leeds University. There are now four Chairs in the specialty in the United Kingdom.

Dr Wright has been Head of the Rheumatism Research Unit at the Leeds University School of Medicine for

The following papers were presented.

D. B. Myers and D. G. Palmer (*Dunedin*) Joint compliance
T. C. Highton (*Dunedin*) and L. Donaldson and W. Bertaud (*Lower Hutt*) Scanning electron microscopy of synovial membrane

J. K. Laing (*Christchurch*) Septic arthritis in rheumatoid disease

B. Tait (*Hamilton*) Sensory trigeminal neuropathy in connective tissue diseases

B. L. J. Treadwell and E. W. Pomare (*Wellington*) Sustained release aspirin—A preliminary report

W. J. Weston (*Lower Hutt*) Radiographic anatomy of the digital flexor tendon sheaths

R. D. Wigley, A. Craig, K. Williamson, K. G. Couchman, and R. Maule (*Palmerston North*) Electronmicroscopy of PN mice showing virus-like particles

D. E. Caughey (*Auckland*) Hypothyroidism and joint disease

J. K. Laing (*Christchurch*) Still's disease in an adult

D. G. Palmer and T. C. Highton (*Dunedin*) Preliminary observations on measuring gold levels in patients with rheumatoid arthritis

J. M. Tweed (*Wellington*) Double-blind trial of Ibuprofen in rheumatoid disease

D. G. Palmer (*Dunedin*) Syncytial masses in cultures of synovial tissues involved by rheumatoid disease

A. G. Wasmuth (*Dunedin*) Biology and genetics of the disease rheumatoid arthritis

some years and is a leading authority on the mechanics of joint movement and lubrication.

He is a member of the Editorial Committee of the *Annals of the Rheumatic Diseases* and is Chairman of the Education Sub-Committee of the Arthritis and Rheumatism Council for Research.

Dr. H. L. F. Currey

Dr H. L. F. Currey has been appointed Reader in Rheumatology at the London Hospital Medical College.

Dr Currey's research interests lie in a number of fields, particularly that of experimental arthritis and its modification by various drugs.

He is a member of the Editorial Committee of the *Annals of the Rheumatic Diseases* and serves on the Scientific and Education Sub-Committees of the Arthritis and Rheumatism Council.

South-East Asia and Pacific area league against rheumatism

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Further information may be obtained from the SEAPAL Secretary-General, Dr I. C. Isdale, Queen Elizabeth Hospital, P.O. Box 513, Roturoa, New Zealand.

Correction

In the paper by R. Arinoviche and G. Loewi (*Annals*, 1970, 29, No. 1, January), on p. 32, it should be noted

that 'Imuran' is the trade name for Azathioprine, which is owned by The Wellcome Foundation Ltd., and not by British Drug Houses, as indicated.