RHEUMATOID ARTHRITIS TREATED WITH "IRGAPYRIN"

ANALYSIS OF 20 CASES

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The treatment of rheumatoid arthritis appears to have been based on empirical considerations because of the lack of accurate knowledge of its aetiology and pathogenesis; numerous remedies have been used, but none has stood the test of time. Hench (1938) observed that rheumatoid arthritis has two sharply contrasting characters, potential chronicity and potential reversibility. He was, however, attracted by the remissions (though temporary) which frequently occurred in pregnancy and also during an attack of coincidental jaundice. This led to the idea that within the body there is a corrective factor, which apparently lies dormant in rheumatoid arthritis, but can be stimulated to function by appropriate methods. Hench and others (1949) obtained striking relief of symptoms by using Compound E in appropriate doses. It was also found that adrenocorticotrophic hormone of the anterior pituitary gland, whose chief function is to stimulate the adrenal cortex, gave a response qualitatively and quantitatively similar to those obtained by the use of Compound E. It is known that under non-specific "stress" the pituitary gland liberates adrenocorticotrophic hormone, which in turn stimulates the adrenal cortex to secrete cortical hormones. Thus "stress" may act as an indirect method of stimulating adrenal cortical secretions. It is further presumed that non-specific agents which are effective in rheumatoid arthritis bring about the amelioration of symptoms by stimulating the pituitary-adrenocortical system. It is postulated that "stress" by non-specific stimulation acts through the mediation of an intact pituitary-adrenocortical system.

On the above hypothesis an attempt has been made to find out the mechanism of action of "Irgapyrin" (3,5-dioxo-I, 2-diphenyl-4-n-butyl-pyrazolidin-dimethylamino-phenyldimethyl-pyrazolon).

Materials and Methods

When the patients were admitted to hospital the total circulating eosinophils were counted by the technique of Randolph (1949). The fall of circulating eosinophils 4 hours after "Irgapyrin" was injected was taken as an index of the activity of the pituitary-adrenocortical system. During this period no other type of treatment was used. The results are summarized in Table I (opposite), which shows a significant reduction in eosinophils 4 hours after the "Irgapyrin" injection (this would occur by chance only once in 1,000 experiments). On further analysis it is seen that patients with less than 50 per cent. reduction in eosinophils showed little improvement in their symptoms. Having seen the difference in response after injecting "Irgapyrin" we thought of correlating the duration of the disease, the percentage reduction in eosinophils, and the clinical response.

The summary in Table II (opposite) shows that there is a distinct relationship between the percentage reduction in eosinophils and the clinical improvement. Patients in whom there was a reduction in eosinophils of more than 50 per cent. showed a remarkable clinical response, whereas those having less than 50 per cent. reduction in eosinophils responded only slightly.

Discussion

"Stress" brings about, perhaps by sympathetic stimulation, a release of adrenaline from the adrenal medulla (Long and Miles, 1950; Recant and others, 1950), and this stimulates the pituitary *via* the hypothalamus (Harris, 1947, 1948; De Groot and Harris, 1950). On stimulation, the pituitary gland liberates the adrenocorticotrophic hormone, which in its turn activates the adrenal cortex (Vogt, 1950) to secrete several types of hormones with specific actions. Of these the glucocorticoids which ameliorate the symptoms are the most important.

The results show a relationship between the percentage reduction of the circulating eosinophils and

RHEUMATOID ARTHRITIS TREATED WITH "IRGAPYRIN"

33

TABLE I
TOTAL EOSINOPHILS IN PERIPHERAL BLOOD
(A) BEFORE AND (B) FOUR HOURS AFTER
INJECTION OF "IRGAPYRIN"

Case No.	Age	Sex	Total Eosinophils (per thousand c.mm.)		Percentage Reduction in Eosinophils	Clinical Response
			(A)	(B)		
1	26	F	218	100	-54.1	Partial improvement
2	24	F	212	72	-66.03	Improvement
3	35	F	167	62	-62.8	Improvement
4	25	F	156	71	-54.48	Partial improvement
5	35	F	385	119	-69.09	Improvement
6	26	M	138	54	-60.8	Improvement
7	36	M	110	25	-77.2	Improvement
8	18	F	418	312	-24.08	No improvement. Patient developed toxic symptoms
9	35	F	118	72	-38.9	No improvement
10	38	F	251	26	-89.6	Improvement
11	16	M	242	173	-28.0	No improvement
12	19	F	218	110	-49.5	No significant change
13	20	F	156	71	-54.4	Partial improvement
14	25	F	142	51	-64.0	Partial improvement
15	22	F	150	40	-73.3	Improvement
16	28	F	148	85	-42.5	No significant improvement
17	20	M	120	42	-65.0	Improvement
18	28	F	136	51	-62.5	Partial improvement
19	25	F	170	60	-64.7	Improvement
20	24	F	110	98	-11.9	No improvement. Patient developed toxic symptoms
Mean			188.25	84.7	-55.65	
S.E.			18.79	14.2	4.22	
"t"			4.42			
p			0.001			

There is a significant reduction in the circulating eosinophils 4 hours after the injection of "Irgapyrin". This will occur through chance alone in 1 : 1,000 experiments.

TABLE II
RELATION BETWEEN REDUCTION IN EOSINOPHILS
AND CLINICAL IMPROVEMENT

Group	Number of Cases	Duration of Disease prior to Treatment	Mean reduction of circulating Eosinophils (percentage)	Clinical Response (percentage)
1	9	4-6 months	-69.83	100
2	5	8-10 months	-57.89	60
3	2	1-1½ years	-46	20
4	4	2-2½ years	-25.72	Nil

the amelioration of symptoms (Table I). This reduction following "Irgapyrin" is also related to the duration of the disease (Table II). On closer analysis

we find that nine cases (Group 1) in whom the duration of the disease varied from 4 to 6 months, had 69.83 per cent. reduction in their total circulating eosinophils four hours after the injection of "Irgapyrin", and in these patients the drug brought about almost complete relief from pain and muscular stiffness. The soft tissue swelling around the affected joints also improved though it did not completely disappear. Five cases of longer duration (8-10 months, Group 2) had a 57.89 per cent. fall in circulating eosinophils. The improvements were less marked; the pain and tenderness did not completely subside, some residual stiffness of the affected joints remained. Although "Irgapyrin" produced amelioration of the symptoms in these cases, it had no effect on the organic changes already established in the joint structures and soft tissues. Group 3, patients who had suffered for over 12 months, had a 46 per cent. reduction in the circulating eosinophils and no significant amelioration of symptoms. In Group 4, patients who had a history of disease going back for 2½ years, "Irgapyrin" therapy did not produce any significant reduction of circulating eosinophils or any improvement in symptoms. It is found that in chronic, long-standing cases, "Irgapyrin" produced hardly any statistically significant reduction (25 per cent.) either on circulating eosinophils or clinical symptoms. Our observations have been limited to a short period, and further observations (both on human rheumatoid arthritis and on experimental arthritis of animals) are necessary before any definite conclusions can be arrived at.

Summary

The amelioration of symptoms by "Irgapyrin" was directly proportional to the duration of the disease. The cases which improved showed a statistically significant reduction in the circulating eosinophils 4 hours after "Irgapyrin" injection. This suggests that the drug acts by stimulating the pituitary-adrenal system. Patients who did not improve after this therapy did not respond to stimulation of the pituitary-adreno-cortical system as there was no fall in circulating eosinophils.

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Arthrite rhumatismale traitée par "Irgapyrin"

RÉSUMÉ

L'amélioration des symptômes produite par l'"Irgapyrin" fut directement proportionnelle à la chronicité de la maladie. Les cas améliorés présentèrent une réduction statistiquement significative du taux des éosinophiles circulants 4 heures après l'injection. Ceci suggère que ce médicament agit en stimulant le système adrénopituitaire. Les malades qui ne se trouvèrent pas améliorés après le traitement ne répondirent pas à la stimulation du système cortico-adrénopituitaire, comme le témoigne l'absence de la chute éosinophile circulatoire.

Artritis reumatoide tratada con "Irgapyrin"

SUMARIO

La mejoría sintomática producida con "Irgapyrin" fue directamente proporcional a la cronicidad de la enfermedad. Los casos mejorados presentaron una reducción estadísticamente significativa de los eosinófilos circulantes 4 horas después de la inyección. Esto sugiere que el producto ejerce su acción por la estimulación del sistema adreno-hipofisario. Los enfermos que no acusaron mejoría después del tratamiento tampoco respondieron a la estimulación del sistema cortico-adreno-pituitario, ya que no se produjo en ellos la disminución de los eosinófilos circulantes.