A STUDY OF THE INTERRELATIONS OF RHEUMATOID ARTHRITIS AND DIABETES MELLITUS

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In investigations on the interrelations of rheumatoid arthritis and the various endocrine disturbances, very little attention has been paid to diabetes mellitus. Thus, there exist only short notes on the occurrence of rheumatoid arthritis among diabetics (Wolf, 1936), and only the effects of an insulin treatment given to rheumatoid arthritis patients have been subjected to a closer examination (Copeman, 1946). A further reason for analysing the interrelations of rheumatoid arthritis and diabetes mellitus was that an increased secretion of the *adrenocortical glucocorticoids* (as cortisone or Compound E) and of the *antehypophyseal hormones* (ACTH) is at present regarded as a feature of diabetes mellitus; and these hormones are those upon which the interest in rheumatoid arthritis is now concentrating.

Material

The study comprises the rheumatoid arthritis and diabetes mellitus patients treated at the Third Medical Clinic of the University of Helsinki and in the medical wards of the Kivelä Hospital during the 15-year period 1934-1948.

Rheumatoid Arthritis Patients.—There were 1,008 in this group, of whom 725 were female and 283 male. The average age in the whole group was 48·7 years.

Diabetes Mellitus Patients.—There were 766 altogether, of whom 490 were female and 276 male. The average age was 51·6 years.

Rheumatoid Arthritis and Diabetes Mellitus occurring in the same Patient

In the present series, $1\cdot3\pm0\cdot36$ per cent. of the rheumatoid arthritis patients were affected with diabetes mellitus, and $1\cdot7\pm0\cdot47$ per cent. of the diabetes mellitus group suffered from rheumatoid arthritis.

In order to know whether the present results show that these two diseases have a tendency either to occur together more often than is due to pure chance, or to avoid each other, the figures should be compared with the corresponding morbidity rates among similar population groups.

According to earlier studies (Järvinen, 1950) the frequency of rheumatoid arthritis in Helsinki is $0\cdot94\pm0\cdot35$ per cent. in control material, corresponding in sex distribution with the diabetes group in question. However, the average age in this control group was only 36 years. In view of the studies of the age distribution

of rheumatoid arthritis (Edström, 1939), the frequency of rheumatoid arthritis will be expected at approximately 1·8 per cent. in the diabetes group in question (average age 51·6 years). This figure corresponds with earlier studies in Finland (Holsti and Rantasalo, 1936).

Among the control material there occurred $0\cdot54\pm0\cdot27$ per cent. of diabetes mellitus. This control group consisted of the cases of typhoid, paratyphoid, and acute gastro-enteritis which were treated in Kivelä hospital from 1934 to 1948. They totalled 748 persons of whom 522 were female and 226 male, the average age being 35·9 years. According to the age- and sex-distribution tables of Joslin and others (1947) this result corresponds with a diabetes frequency of 1·4 per cent. in a group of an average age of 48·7 years, in which approximately three-quarters are women. This figure approximates to those given in studies on the frequency of diabetes mellitus in various countries (Joslin and others, 1947).

Result.—As is shown above, $1\cdot3\pm0\cdot36$ per cent. of the patients of the present series suffering from rheumatoid arthritis were also affected with diabetes mellitus, whereas the occurrence of diabetes mellitus in a corresponding group was assessed at 1·4 per cent. $1\cdot7\pm0\cdot47$ per cent. of the diabetes mellitus patients of the series suffered from rheumatoid arthritis, whereas the estimated occurrence of rheumatoid arthritis in a corresponding group of people was approximately 1·8 per cent.

Considering the many sources of error (it must be noted, for instance, that the study was concerned only with hospital patients), the present results show at least that these two diseases have no obvious tendency either to occur together, or to avoid each other.

Mutual Effects of Rheumatoid Arthritis and Diabetes Mellitus occurring in the same Patient

Rheumatoid arthritis and diabetes mellitus occurred in the same patient in thirteen of the present cases. An attempt has been made to elucidate the inter-relations of these two diseases with the aid of the Table overleaf.

Among the patients affected with both rheumatoid arthritis and diabetes mellitus, were some in which the rheumatoid arthritis began first and some in which the diabetes mellitus began first. *In most cases, the disease first acquired appeared to proceed as before, unaffected by the new illness.* In two cases, there was a distinct exacerbation of the symptoms of rheumatoid arthritis at the onset of diabetes mellitus. Conversely, in one case, diabetes mellitus was aggravated by the onset of rheumatoid arthritis. It must also be noted that, in one case, both diseases seemed to appear at the same time.

Discussion

At the present time, it is usually thought that in many cases of diabetes mellitus, the secretion of the antehypophyseal hormones, in particular that of ACTH, and of the adrenocortical glucocorticoids is increased. This is regarded as being especially

true of the type of diabetes which begins in middle age, and is associated with obesity and arterial hypertension. In addition to the numerous investigations supporting this view which have been presented in the textbooks, it may be mentioned that, analogously with the earlier animal experiments, it has recently been noted that ACTH as well as cortisone is able to produce symptoms of diabetes mellitus in man (Boland and Headley, 1949; Brøchner-Mortensen and others, 1949; Conn and others, 1948).

TABLE
PATIENTS AFFECTED WITH BOTH RHEUMATOID ARTHRITIS AND DIABETES MELLITUS

Groups of Patients		Rheumatoid Arthritis began first (7)							Diabetes Mellitus began first (5)				Both diseases began simultane- ously (1)	
Sex		M.	M.	F.	F.	F.	F.	F.	F.	F.	F.	F.	M.	F.
Age	at onset R.A. of	34	35	36	43	44	51	53	53	53	58	60	61	60
	at onset D.M. of	62	63	38	72	48	54	65	49	40	48	44	56	60
Use of insulin		No	at times	at times	No	contin- uously	No	at times	at times	contin- uously	No	No	at times	at times
Height (cm.)		173	182	153	154	Thin	170	Fat	162	165	157	162	170	158
Weight (kg.)		90.5	75	66.3	67.5		69		66	61.5	54.9	105	74.9	61
Blood pressure (mm. Hg)		160/110	180/100	220/110	150/80	120/80	160/110	160/110	240/120	160/100	250/120	205/110	190/90	130/70
R.A. with obvious active swellings in joints during D.M.		No	Yes	No	No ?	Yes ?	Yes	Yes ?	Yes	Yes	Yes	Yes ?	Yes	Yes
Changes in first disease at onset of the second disease		0	+	0	0	0	+	0	+	0	0	0	0	+

0=no changes.

+ =activation of symptoms.

Therefore it may be assumed that the secretion of the antehypophyseal hormones (ACTH) and of the adrenocortical glucocorticoids (cortisone) has been pathophysiologically increased in at least some of the thirteen diabetes-rheuma patients (most of whom suffered from the type of diabetes commencing in middle age), and is associated with obesity and arterial hypertension (this was seen in seven distinctly, and four somewhat less clearly).

On the other hand, the present investigations show that the onset of diabetes mellitus did not effect a recovery from a simultaneous rheumatoid arthritis, and did not even prevent the onset of rheumatoid arthritis. This finding suggests that even a pathophysiologically increased secretion of ACTH and of glucocorticoids (cortisone) has no curative effect on rheumatoid arthritis.

Thus it seems strange that a rapid recovery from the symptoms of rheumatoid arthritis can be effected by administering *massive* doses of ACTH or cortisone, as has been shown by the revolutionary experiments of Hench and others (1949).

It is, therefore, advisable to think that the *manifest effects of massive doses of these hormones depend on something other than their simple physiological hormonal actions*. This is suggested also by the experience of Hench and others (1949) that smaller doses of these hormones have no curative effect.

In studying the difference between the physiological action of these hormones and the effect of massive doses of them, it is worth noting that, *in connexion with a massive administration of ACTH or cortisone to rheumatic patients, the development of symptoms suggesting an atrophy of the adrenal cortex has been observed*, corresponding to the results of animal experiments (Sprague and others, 1950). From this observation a parallel may be drawn between the advantageous effects of massive doses of cortisone and the theories of Selye (1946). The increased secretion of the mineralocorticoid, desoxycorticosterone, which Selye regards as an essential factor in the aetiology of rheumatism, would be reduced by the atrophy of the adrenal cortex caused by massive doses of cortisone and thus a favourable effect would be obtained.

Summary

(1) The interrelations of rheumatoid arthritis and diabetes mellitus have been studied in 1,008 cases of rheumatoid arthritis, and 766 cases of diabetes mellitus. An analysis of this material suggests that the occurrence of these two diseases in the same person corresponds with the average occurrence of both the diseases in the population in general. Accordingly, these diseases seem to have no tendency either to occur together or to avoid each other.

(2) Thirteen cases, in which the same patient was affected with both rheumatoid arthritis and diabetes mellitus, were subjected to a more detailed analysis: in nine there was no evidence of a mutual effect of the diseases upon each other; in two cases of rheumatoid arthritis, the symptoms were aggravated simultaneously with the onset of diabetes mellitus; in one case of diabetes mellitus the symptoms were exacerbated at the onset of rheumatoid arthritis. In one case, both diseases began at the same time.

(3) The present findings (which show that diabetes mellitus seems to have at least no curative action on rheumatoid arthritis) are compared with the modern view, according to which diabetes mellitus is closely associated with an increased secretion of the anterior hypophyseal adrenocorticotrophic hormone (ACTH), and of the adrenocortical glucocorticoids (as cortisone). Since, however, massive doses of ACTH and cortisone are known to give rapid relief to the symptoms of rheumatoid arthritis, the writer's interpretation is that these hormones have a different action according to whether they are administered in physiological or in massive doses. An attempt is made to explain this difference by the suggestion that the massive dosage of these hormones acts on rheumatoid arthritis through those disturbances which it is known to cause in the hormonal secretions of the organism.

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Étude du Rapport entre l'Arthrite Rhumatismale et le Diabète Sucré

RÉSUMÉ

(1) Cette étude porte sur 1,008 cas d'arthrite rhumatismale, et sur 766 cas de diabète sucré. L'analyse de ce matériel suggère que l'incidence de ces deux maladies chez les mêmes sujets correspond au multiple de leur incidence respective générale, c'est à dire qu'elles n'ont pas tendance à se présenter ensemble ni à s'éviter.

(2) L'analyse détaillée de treize cas d'arthrite rhumatismale et de diabète sucré coëxistant chez le même sujet ne révéla aucun indice d'influence d'une maladie sur l'évolution de l'autre dans neuf cas; dans deux cas d'arthrite rhumatismale il y eut une aggravation des symptômes coïncidant avec le début du diabète; dans un cas de diabète sucré les symptômes s'aggravèrent au début de l'arthrite rhumatismale; dans un cas les deux maladies débutèrent en même temps.

(3) On discute ces résultats (montrant que le diabète sucré ne semble exercer aucune action curative sur l'arthrite rhumatismale) à la lumière des conceptions modernes, selon lesquelles le diabète serait étroitement associé à l'augmentation de la sécrétion de l'hormone adrénocorticotrophique pituitaire antérieure (ACTH) et des glucocorticoïdes surréniaux, comme le cortisone. Sachant, cependant, que des doses massives de l'ACTH et du cortisone font disparaître rapidement les symptômes de l'arthrite rhumatismale, les auteurs pensent que l'action de ces hormones en doses physiologiques diffère de leur action en doses massives. Pour expliquer cette différence on suggère que les doses massives de ces hormones agissent sur l'arthrite rhumatismale par le fait qu'ils provoquent le dérangement bien connu des sécrétions hormonales de l'organisme.

Estudio de la Relacion entre la Artritis Reumatoide y la Diabetes

RESUMEN

(1) Este estudio comprende 1,008 casos de artritis reumatoide, y 766 casos de diabetes. El análisis de este material parece mostrar que la incidencia de ambas enfermedades en un sujeto corresponde a su incidencia general y que, por consiguiente, estas enfermedades no tienen tendencia a presentarse juntas ni a evitarse.

(2) Se ha estudiado con interés particular trece casos de coexistencia de la artritis reumatoide y de la diabetes en el mismo sujeto. En nueve casos no se encontró indicios de influencia de una de estas enfermedades sobre la evolución de la otra. En dos casos de artritis reumatoide hubo agravación de síntomas coincidente con el principio de la diabetes. En un caso los síntomas de la diabetes empeoraron al principiar la artritis reumatoide. En un caso ambas enfermedades empezaron al mismo tiempo.

(3) Se discute estos resultados (mostrando que la diabetes no parece ejercer acción curativa alguna sobre la artritis reumatoide) en relación con las concepciones modernas según las cuales la diabetes estaría estrechamente liada al incremento de la secreción de la hormona adrenocorticotrófica hipofisaria anterior (ACTH) y de los glucocorticoides suprarrenales, como el cortisón. Sabiendo, sin embargo, que dosis fuertes de ACTH y del cortisón alivian rápidamente los síntomas de la artritis reumatoide, se considera que estas hormonas ejercen una acción diferente según se las administra en dosis fisiológicas o en dosis fuertes. Para explicar esta variación de efectos se sugiere que dosis fuertes de estas hormonas actúan sobre la artritis reumatoide como consecuencia del conocido disturbio de las secreciones hormonales del organismo.