CAN THE DEFENCE MECHANISM OF THE BODY BE INFLUENCED BY ROENTGEN IRRADIATION ?

REPORT ON A PRELIMINARY CLINICAL INVESTIGATION OF THE PLASMA OR SERUM PROTEIN PATTERN IN RHEUMATOID ARTHRITIS

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Plan of Investigation

The profound effect on the organism of relatively small doses of x-rays (5 to 50 r) have been known for some time, and such small doses have been used empirically in infective and allergic conditions.

To investigate the biological properties of x-rays it was decided to study the possible effects of small doses of radiation on the resistance of the body, and for this purpose it was considered that patients with rheumatoid disease were suitable types. The plan decided upon was in four sections : (1) soft radiation (50 kV) to the trunk (this is mostly absorbed in the skin) ; (2) penetrating radiation (200 kV) to the trunk in the same "volume dose" as given by the soft radiation ; (3) penetrating radiation (200 kV) to the trunk of the same "surface dose" as the soft radiation ; (4) penetrating radiation locally in the same "volume dose" as in (1) and (2).

The surface dose given in (1) was decided upon with the view to the volume dose given in (3) being tolerable to the patient. It was intended to proceed in the same patient from one scheme to the others in the order given, and to note the effect both clinically and through various laboratory investigations which might provide indications of favourable or unfavourable effects of the treatment.

The following paper is an account of the first stage of the scheme, presented because of the interesting findings of evidence of the effects of the radiation used on the plasma and serum proteins, and the relation of this effect to the clinical progress of the patients.

Although no satisfactory definition of the term "natural defence mechanism of the body" can yet be given, it is generally believed that such a mechanism exists. Any functional or organic deviation from normal, whether internally or externally caused, brings into action a defending, repairing, or balancing system within the body. While little is known about the actual mechanism, it is thought that most

important roles are played by the reticulo-endothelial system (R.E.S.), the liver, and the blood proteins.

In order to demonstrate the influence, if any, of wide-field irradiation with soft x-rays on the defence mechanism it is necessary to find some entity which is a part of this mechanism and at the same time amenable to objective observation. It has been stated in the literature (see below) that low albumin and high globulin values are frequently found in cases of rheumatoid arthritis. An investigation of these proteins was therefore begun.

It was fortunate that the first cases showed very low albumin and high globulin values, and that after the first irradiations there was a significant turn towards more normal values. This happened before any clinical signs of improvement set in ; and, thus encouraged, the tests were continued until clinical improvement could be observed. Subsequent results and the work of other investigators tend to confirm that the plasma or serum protein pattern shows a reliable correlation with at least one important part of the body's defence mechanism.

So far nine cases of rheumatoid arthritis have been treated by means of this wide-field technique, using soft x-rays (50 kV), H.V.L. 0.33 mm. aluminium, and doses of 5 to 50 r weekly for four to eight weeks (details are given with the charts). All patients had advanced disease that had previously failed to respond to standard treatments. In each case detailed clinical observation was combined with blood analyses of albumin, globulin, fibrinogen, erythrocyte sedimentation rate (E.S.R.), haemoglobin estimation, blood count and blood picture, before treatment and at intervals during and after the irradiation treatment. The results seem interesting enough to justify a preliminary report even though it is based on only these nine cases. Unfortunately each investigation is bound to be very lengthy and the capacity of a laboratory to handle many tests is limited.

TABLE 1

DETAILS OF NINE CASES

Case	Sex	Age (yrs.)	Before treatment			Best condition realized			Relapses			Intercurrent disease (no relapse in rheum. arth.)		Latest observation			Liver tests	
			Clinically*	Alb.	Glob.	Clinically	Alb.	Glob.	Clinical deterioration to	Alb. fall to	Glob. rise to	Alb. fall to	Glob. rise to	Clinically	Alb.	Glob.	Thymol turbidity	Cephalin cholesterol
1	F.	54	10.2.1948 S ⁺ III	2.7 —	2.9 (+)	S ⁺ I	4.48 norm.	2.1 norm.				3.9 —	3.4 ++	22.12.1948 S ⁺ I	4.3 norm.	2.5 norm.	neg.	neg.
2	F.	54	12.2.1948 S ⁺ III	3.0 —	3.2 ++	S ⁺ II	4.1 low norm.	2.5 norm.	S ⁺ III	3.4 —	3.3 ++			5.1.1949 S ⁺ II	3.9 near norm.	2.7 high norm.	neg.	neg.
3	F.	45	12.2.1948 S ⁺ III	3.4 —	3.2 ++	S ⁺ II	4.5 norm.	2.3 norm.	S ⁺ III	3.8 —	3.0 (+)			14.12.1948 S ⁺ II	4.5 norm.	2.3 norm.	neg.	neg.
4	M.	50	29.1.1948 S ⁺ III	3.4 —	3.0 (+)	S ⁺ I	4.0 low norm.	2.4 norm.				3.4 —	3.1 ++	5.1.1949 S ⁺ I	4.0 low norm.	2.5 norm.	neg.	neg.
5	M.	39	12.4.1948 S ⁺ III	4.2 norm.	2.4 norm.	S ⁺ III	lower than before treat.	higher than before treat.	NO REMISSION					10.11.1948 S ⁺ III	3.0 —	3.47 ++	11.10.48 13 units 10.11.48 14 units congo red test negative	floccul. ++ floccul. ++
6	F.	39	23.3.1948 S ⁺ III	3.9 near norm.	2.4 norm.	S ⁺ II	4.48 norm.	1.98 norm.	S ⁺ III	3.3 —	3.2 ++			5.1.1949 S ⁺ II	4.0 low norm.	2.6 norm. (+)	25.10.48 4.5 units 25.11.48 4.3 units 8.12.48 4.0 units 5.1.49 5 units	neg. neg. neg. neg.
7	F.	24	8.1.1948 S ⁺ III	2.6 —	3.9 ++	S ⁺ I	4.5 norm.	2.4 norm.	S ⁺ III	3.3 —	3.2 ++			23.12.1948 S ⁺ I	4.4 norm.	2.7 high norm.	neg.	neg.
8	M.	58	12.7.1948 S ⁺ III	3.9 near norm.	2.5 norm.	S ⁺ III	4.0 low norm.	higher than before treat.	S ⁺ III	3.8 —	3.7 ++			4.1.1949 S ⁺ III	3.8 —	3.0 (+)	22.10.48 12.5 units 24.11.48 8.0 units 4.1.49 8.0 units	C-reactive protein floccul. ++ floccul. ++ floccul. ++
9	M.	62	9.2.1948 S ⁺ III	2.9 —	3.1 ++	S ⁺ II	4.7 norm.	2.5 norm.	S ⁺ III	4.0 low norm.	3.1 ++			30.12.1948 S ⁺ II	4.3 norm.	2.6 norm. (+)	neg.	neg.

TABLE 2
MODIFICATION OF TEGNER'S "THREE CLINICAL STEPS"
(Key to Table 1)

I	Quiescent	1. Systemically and locally quiescent.	
		2. Locally slight occasional pain, systemically quiescent.	
II	Active	1. Systemically	a : quiescent, no travelling symptoms.
			b : slight symptoms, travelling.
		2. Locally	a : occasional pain.
			b : continuous pain.
III	Very Active	1. Systemically	a : active and travelling.
			b : very active, travelling, burning.
		2. Locally	a : active, very manifest.
			b : very active, manifest, and crippling.

The material below is arranged as follows : (1) a brief account of the albumins and globulins in the blood, in normal condition and in disease ; (2) the possible aetiology and a short survey of rheumatoid arthritis ; (3) a note on soft roentgen therapy ; (4) short notes on the cases, illustrated by charts and a comparative table ; (5) a discussion of the findings ; (6) summary and conclusions.

Significance of Blood Protein Movements.—The normal ranges for the different plasma or serum proteins vary from author to author, depending on the method of investigation used and probably on the clinical material. The charts are based on the normal ranges given by Kolmer (1944).

It is important that the tests be made under the same conditions, in the same laboratory, and by the same chemist to secure standard methods as far as possible. Such a standard laboratory technique (Howe's method of salting out by Na_2SO_4) was applied. To ensure complete digestion in the Kjeldahl method selenium dioxide was used as a catalyst and digestion was continued for three and a half hours (Hoch and Marrack, 1945). It should be noticed, however, that at the beginning of the investigation the plasma proteins were used, whereas after June 1948 the serum proteins were used, in order to avoid variations arising from a water shift from the erythrocytes to the plasma, due to the oxalate used as anticoagulant.

Deviation from the normal protein pattern is unspecific, but any fluctuation of the proteins reflects the organism's changing ability to react (Wuhrmann and Wunderly, 1947, p. 144). In other words, as Stern and Reiner (1946) express it, the value of electrophoresis does not lie in the specificity of its pattern for given diseases : rather, the pattern provides information on the pathological state of the organism as a whole. There exists a close correspondence between the blood, the protein system, and the general state of health, even though

there is no clear correspondence with a given pathological condition.

In rheumatoid arthritis we frequently find decrease of albumins and increase of globulins, relative or absolute, and consequently the albumin-globulin ratio is low.*

It has been found† that arrested cases of rheumatoid arthritis show a return to substantially normal albumin and globulin levels, and that treatment resulting in clinical improvement is indicated by a tendency to return to normal. Swedin and Bengtsson also observed a reduction of a previously increased fibrinogen.

Rheumatoid Arthritis.—Rheumatoid arthritis (or rheumatoid disease, a name suggested lately with very good reason by Ellman and Ball, 1948) is a systemic disease of unknown aetiology. Many workers suspect that rheumatoid arthritic patients become sensitized through some allergen and that, in fact, they are in a state of allergy in which the most obvious manifestations are pathological reactions of mesenchymal tissues. So far this is only a theory, but it is based on sound and reasonable observation and can probably explain the manifold symptoms of the disease. This theory is discussed in all modern textbooks on rheumatoid arthritis.‡

Even more various than the suspected causes of rheumatoid arthritis are the therapeutic measures which have been and are taken against the disease. Recently in his Samuel Hyde lecture Hench (1948) gave an impressive critical survey of them. General

* Wuhrmann and Wunderly, 1947, p. 276; Malmros and Blix, 1946; Svartz, 1943, 1944; Luetscher, 1947; Gutman, 1948; Loevgren, 1945.

† Gutman, 1948, p. 219; Dole and Rothbard, 1947; Swedin and Bengtsson, 1944; Perlmann and Kaufman, 1946; Malmros and Blix, 1946; Luetscher, 1947.

‡ Copeman, 1948; Comroe, 1944; Dawson, 1935; Ellman, 1947; Tegner, 1948; Loevgren, 1945; see also the American Rheumatism Association *Primer on Arthritis*, 1942.

FIG. 1.—Case 1. A woman aged 54 years. This patient's menopause was in 1939, and rheumatoid arthritis began in 1940; hands (stigmatized), wrists, and knees were affected.

supporting treatment together with chrysotherapy seems to give the best results at present, but it is clear that local treatment is far less important than systemic treatment as long as the disease has not become quiescent or "burnt out".

Soft Roentgen Therapy.—Roentgen therapy has probably been tried in every conceivable form of disease, and the immense progress with deep x-rays, especially in malignant disease, has completely overshadowed low-dosage, longer-wave treatment. But time and again during the last decades we find publications stressing the beneficial action of softer irradiation, especially for inflammation and for desensitization. Some authors suspected a stimulation of the body's defence mechanism. If such

a beneficial influence on the systemic defence mechanism could be proved and more thoroughly explored, we might establish a most potent therapeutic agent of great importance to medicine in general.*

Whereas deep x-ray treatment is scientifically well founded, in spite of many theories no entirely convincing scientific proof for the mode of action of soft irradiation has been demonstrated. Even with clinical results in many cases as good, or even better, than orthodox treatment, general medical opinion

* The literature is too abundant to be mentioned in full, but fundamental work has been connected with the names of Murphy and Nakahara (1922), Scott (1939), Hernaman-Johnson (1926), Bucky (1929, 1944), Hodges (1936), Denier (1936), Medinger and Craver (1942), Holthusen (1940), Cameron (1941), Finzi (1947), Finzi and Freund (1943), Freund (1947), Kelly and Dowell (1942), and MacKee and Cipollaro (1946).

FIG. 2.—Case 2. A woman aged 54 years. The patient's mother was crippled with rheumatoid arthritis for the last twenty-five years of her life. The patient's menopause was in 1945, with onset of rheumatoid arthritis type poly-arthritis. Hands, wrists, elbows, shoulders, neck, knees, and gait were affected. She was stigmatized and crippled.

has frowned on it as near charlatantry. The only established and acknowledged place which softer irradiation with x-rays has found in therapy is in dermatology. It was from experience in this branch of medicine, years ago, that the author was held by the idea that in softer x-ray irradiation over wide fields we may have a means of indirectly stimulating the defence mechanism of the body.

Notes on the Cases

For lack of space no detailed case histories can be given, but all essential information can be obtained from the charts and Table 1.

To assess clinical states and changes Tegner's three clinical steps have been used, modified, so as to distinguish

as far as possible between systemic and local conditions. It is considered that the symptoms are essentially systemic when the patient looks toxic (pale grey to yellowish) and is of low morale, and when the symptoms are travelling, that is, switching from one place to another (although such patients have at the same time sites of predilection where local symptoms are constantly present, changing only in degree). Further it is considered a systemic symptom when the pain not only radiates into the surroundings of an affected joint, but seems also to affect the whole length of a limb or the region of a nerve. One of the very active systemic stages is described by patients as "burning" pains, often affecting the whole body. An explanation of the clinical classifications is given in Table 2. Details from case histories and results of routine tests (not contained in the charts) will be mentioned only if relevant.

FIG. 3.—Case 3. A woman aged 45 years. In 1944 this patient had herpes zoster; soon afterwards rheumatoid arthritis affected her ankles, later the hands and wrists, and occasionally the sacro-iliac region. In 1946-47 she had orthopaedic treatment for flat feet. In 1947 chrysotherapy was followed by dermatitis. She was stigmatized in hands and feet, and crippled. It is difficult to judge how much of the right ankle complaint remaining is due to mechanical causes (both ankles have been manipulated, with great improvement in the left one but not in the right) and how much to rheumatoid arthritis. There are practically no pathological signs on the radiograph.

In all nine cases the wide-field treatment was carried out with a Philips Contact Therapy set: 50 kV, 0.33 mm. Al H.V.L., no added filter, 2 or 3 mA, 56 cm. f.s.d., field-trunk (30 × 50 cm.), anterior and posterior at each session (total dosage stated is the sum of anterior and posterior doses). Treatment was given once weekly, single doses varying from 5 to 50 r. The dosage may appear small, but in view of the size of the field, roughly one third of the total body surface at each session, the volume dose is not inconsiderable. It was difficult for our physicists to make an accurate estimate of the volume dose for such very soft radiation, but for the field size used they consider it to be of the order of 2,500 g.-roentgens per r at the skin.

Discussion

The difficulty in objectively assessing results due to therapeutic measures is well known in a disease

with spontaneous remissions, sometimes lasting for long periods. Tegner sums up this situation very well in the short phrase: "I never discharge a rheumatoid arthritic." So far we have no means of making sure that the systemic disease has burnt out and that successful desensitization has taken place. In none of the cases described can such an ideal stage be assumed. Nevertheless Table 1 reveals some interesting points.

All nine patients had more or less severe, advanced rheumatoid arthritis and had gone through most forms of treatment without improvement or remissions of any length of time. Of these nine, two are considered clinical failures, and the rest have, at least for some time, made satisfactory clinical progress.

FIG 4.—Case 4. A woman aged 50 years. In 1944 a submaxillary lymph gland was removed (the pathological report diagnosed Hodgkin's disease, at present quiescent) followed by deep x-ray treatment to thorax, anterior and posterior, and neck. In 1946 he had influenza followed by rheumatoid arthritis affecting the hands (stigmatized), arms, shoulders, and occasionally the sacro-iliac region, with pain radiating to the thighs. His mother had been crippled by rheumatoid arthritis for the last twenty years of her life.

Except for variation in the severity of their rheumatoid arthritis the nine patients showed no clinical differences which would have suggested differences in their manner of response. Only in the protein pattern before treatment was there a well marked difference: the two patients who did not respond, and a borderline case showed normal globulin values, and albumin values either normal or only slightly decreased. The patients who improved had markedly decreased albumins and nearly as markedly increased globulins.

It was observed that within two or three weeks of beginning treatment the patients who improved looked better and (if they had done so before) less toxic; the worried expression vanished and morale seemed to improve. During the first weeks the

patient rarely reported any improvement in his condition; on the contrary, sometimes there was more local pain and stiffness following a session and lasting for some hours or up to a week.

The first good sign was a report from the patient that he had had a few hours' or even days' relief from pain. Sometimes such reports were given in the latter part of a course, sometimes only some weeks after the end of the first course. It could be noticed that patients who before treatment made only slow and sparing movements made quicker and more frequent ones on improvement. In contrast to the slow clinical progress the albumins and globulins seemed to respond from the very beginning of irradiation. Improvement in the albumin and globulin curves always preceded clinical improvement.

FIG 5.—Case 5. A man aged 39 years. The patient had psoriasis since 1929, and polyarthritis since 1945. Myochrysine produced no improvement, and the psoriasis became worse. Vaccine treatment aggravated the rheumatoid arthritis. In 1947 he had spa treatment in Bath and deep x-ray therapy to the spine, but without benefit. Arthrodesis was performed on the wrists and arthroplasty to the shoulders. His mother suffers from rheumatism. He himself is crippled and stigmatized in hands, arms, spine, and legs; he can hardly stand, and can walk only a few yards. The haemoglobin is estimated at 64 per cent. (100 per cent. = 14.8 g. haemoglobin per 100 c.cm., error ± 1 per cent.).

After a course of treatment the albumin and globulin pattern continued to improve in cases that responded well, and gradually the curves levelled out. This coincided with the consolidation in clinical improvement. After six to eight weeks' interval a second wide-field course was given, with increased dosage, but the result was generally not encouraging. In any case no consolidation could be observed of ground gained and it might have been better to wait for the further natural development.

Where relapses occurred they were preceded by unfavourable albumin-globulin readings, and a remission was foreshadowed by albumin and globulin curves making a favourable shift again. It has already been mentioned that the low albumin and high globulin pattern is similar in many other diseases (therefore it is unspecific) and only reflects the reactive power of the body. In this connexion it was observed that a shift in the wrong direction in the albumin-globulin pattern could take place without being followed by a relapse. In two such instances the patient had an acute cold, and it may well be that at the time their defence mechanism was lowered and they were more prone to relapse, even if it did not become manifest. In some of the other cases the relapse was associated with an acute cold or pharyngitis.

Case 6 must be regarded as a border line case. She was classed as not responding, but four weeks after a third course with extremely low dosage the albumins and globulins took an unexpected and favourable turn. When the blood sample was taken (Nov. 25, 1948) there was no evidence of clinical improvement, but the laboratory results obtained a few days later seemed to indicate imminent improvement. This was confirmed by the patient on Dec. 8, 1948; her right ankle was still painful and swollen, but the disease in her hands, which had been very active on Nov. 25, 1948, was now completely quiescent and her general condition had improved. The albumin and globulin values of the sample taken on Dec. 8, 1948, were still satisfactory. At the time of writing it is too early to speculate on her dubious liver function (see also below), on the state of her defence mechanism, and on whether this late remission is purely natural or can be attributed to the treatment.

It has been said that the two non-responding cases (Cases 5 and 8) showed normal globulin and near-normal albumin values before treatment. Case 5 even had a normal erythrocyte sedimentation rate (E.S.R.). With these patients the irradiation treatment had no beneficial effect on the albumin-globulin pattern, nor were their complaints relieved for any appreciable time.

The unfavourable shift in the albumin-globulin pattern can be seen clearly in Case 5. In this case it

FIG. 6.—Case 6. A woman aged 39 years. This patient had gonorrhoea in 1936, followed by arthritis in both proximal joints of the big toes. She recovered completely (all tests concerning a possible gonorrhoeal cause in her later arthritic condition have been negative). In 1937 rheumatoid arthritis began in the left foot, and by 1938 it was in both feet and hands. In 1939 hyperthermy brought complete remission until 1943, when she relapsed. In 1943–44 there was a remission during pregnancy, and a relapse six weeks after confinement. Hands (stigmatized), wrists, elbows, knees, and ankles are affected. Her legs are crippled.

took eight weeks after the first course had finished before a slight recovery in the protein pattern took place, but there was no improvement in the patient's condition. A short trial of a second course with extremely low dosage sent the albumin curve down and the globulin curve sharply up, thus ruling out further attempts at irradiation. Case 8 showed the same development, though in a less pronounced way.

Concerning these two non-responding cases, it should be mentioned that during 1947, when a number of cases of rheumatoid diseases were being treated, liver function tests were made on each patient; but this practice was later given up as all the tests proved negative. However, after the unfortunate experience with Case 5, liver tests were made on this patient, with positive results. All nine cases were then subjected to liver function

tests (see Table) and thus the interesting fact was revealed that whereas the six responding cases showed no abnormality the two non-responding cases showed abnormality and Case 6 (the borderline case) showed a dubious result.

Can liver damage have been caused by the x-ray irradiation? The dosage appears to have been far too small, fractionated, and superficial, to have caused a direct damage to the hepatic tissues. Moreover, there were no symptoms of x-ray sickness. It may be that through a pathological liver condition which was established before the x-ray irradiation,* the defence mechanism was

* It may be noted that both these patients had previously had gold treatment (Case 5 three years before, without improvement; Case 8 from 1944 for two years, weekly, that is, for a very prolonged time, but with great improvement). Case 6 (borderline case) had had no previous chrysotherapy.

FIG. 7.—Case 7. A woman aged 24 years. In 1940 polyarthritis began, with remission during pregnancy and a relapse four weeks later. Her whole gait was stigmatized, and her hands were claw-like. Nearly all her joints were affected, especially hands, wrists, elbows, shoulders, spine, hips, knees, and ankles. She was very crippled.

at a low level or exhausted. The existing normal levels for albumin and globulin before treatment refer only to quantity. The question of quality will be dealt with presently. In any case there is good reason for supposing that the functional liver impairment existed even before treatment, since other authors have also drawn attention to the possibility of liver damage in rheumatoid arthritis. Loevren (1945) suspects damage of the liver function, and he states that in ninety-three cases where necropsy had been performed 42 per cent. showed fatty degeneration of the liver, 8 per cent. amyloidosis, 10.7 per cent. cirrhosis. Wuhrmann and Wunderly (1947, p. 238) point out that the prognosis of liver damaged cases in rheumatoid arthritis

is worse, since they show a strong tendency to develop fibrosis, thickening of the capsules, and ankylosis (all typical of Case 5). The same authors (pp. 204, 317) state that the most important site of manufacture and metabolism of all blood proteins is probably the liver. It is likely that the reticulo-endothelial system (R.E.S.) is the main place of formation of globulins, and as a good part of the R.E.S. is contained in the liver, damage to the latter would affect the globulins.

Unger and others (1948) report that rheumatoid arthritis and amyloidosis of the liver co-exist more frequently than is suspected. Amyloidosis was suspected in Case 5, but the Congo red test was negative. It should of course be kept in mind that

even where we do not find gross pathological changes of the liver in rheumatoid arthritis there may be cases of abnormal liver function which our present methods are not able to reveal.¹

With the best available methods we can still obtain only quantitative estimations; as to the quality and functional capability of the protein fractions, we must await further discoveries. In 1938 Kendall stated that neither the albumin nor the globulin fractions are homogeneous: both fractions are mixtures of proteins which have different immunological properties. Luetscher (1947) says rightly that the increased globulin post-immunization is not necessarily identical with normal γ globulin, nor is the increase in the γ fraction entirely active antibody. When the proportions of the serum proteins are altered by disease there may be qualitative changes in the fractions and not simply more or less of the normal proteins.

Holmberg and Groenwall (1942), having the help of Tiselius himself, found a new crystalline serum globulin, not identical with any fraction of normal globulin, in a case of rheumatoid arthritis (with no signs of co-existing myeloma). Dole and Rothbard (1946) described a protein of unknown significance occurring in the serum in various diseases and contained in the α_1 globulin fraction. It is known as c-reactive protein.

Cohn and others (1946) arrived at a separation and purification of protein components which allowed some study of their individual properties and even therapeutic use.

It has been observed that hepatitis with icterus frequently has a favourable influence on rheumatoid arthritis (Hench, 1940). Loevgren (1945) found high values for citric acid and serum iron in hepatitis, and both these values are low in chronic poly-arthritis, but what differences in the serum and plasma protein fractions may be present in rheumatoid arthritis and hepatitis are unknown.

Equally interesting is the not infrequent phenomenon that women with rheumatoid arthritis enjoy a remarkably complete remission during pregnancy until after term (this occurred in Cases 6 and 7). Trials with transfusion of blood of pregnant women into rheumatoid arthritics have been made (Hench, 1938; Barsi, 1947), but opinion is divided on the results. Normal blood transfusions have also been used. Lately Simpson and Hall Brooks (1948) reported on their investigations; they found clinical improvement and at least a temporary return to normal albumin and globulin values.

So far functional liver impairment and a temporarily or permanently lowered (or exhausted)

defence mechanism as possible causes which may influence our therapy have been mentioned, but it is quite obvious that other factors are also involved. Much may depend on the type of patient and on constitutional or acquired differences. Even if we think of rheumatoid arthritis as a manifestation

FIG 8.—Case 8. A man aged 58 years. Rheumatoid arthritis began in the hands in 1943; the patient was benefited by prolonged gold therapy (weekly injections for two years). By 1946 he could work again as a tailor. A relapse in 1947 affected the hands, arms, shoulders, spine, and legs. From January to June 1948 he had deep x-ray treatment to shoulders, hips, ankles, and hands, but without benefit. His hands were stigmatized and crippled.

FIG. 9.—Case 9. A woman aged 62 years. Rheumatoid arthritis began in 1932, and the patient has had nearly continuous treatment since then, including gold and vaccine therapy, but with no improvement. Hands (stigmatized), arms, knees and walk (crippled) are particularly affected.

in a sensitized subject, we should not too readily assume that only one allergen is responsible. There may be more than one causing the same symptoms, and apparently similar cases may not yield to a similar therapy.

Many illnesses have various phases, and the phase at which treatment is given is not irrelevant. In the case of rheumatoid arthritis treated by the wide-field technique described, not only does this apply but the irradiation itself releases a biological action which probably exhibits a phase development. The correct timing of the irradiation with an appropriate dosage is therefore likely to be of utmost importance. Factors such as the quality of radiation, fractionation, and field area are no doubt important also. Clearly much more work will have to be done before approximately optimal con-

ditions for treatment of any individual case can be assessed.

Once the aim has been realized of inducing a favourable systemic effect, possibly of desensitizing the patient, or at least of bringing about a remission, treatment by means of physical medicine or local x-ray application may then prove more successful than if it is given in an acute state of general manifestation of the disease.

To conclude the discussion a word must be said on fibrinogen and on the E.S.R. According to Cantarow and Trumper (1947, p. 86) a moderate increase in fibrinogen is observed in conditions causing slight hepatic injury and tissue destruction, also in pregnancy and menstruation, and following x-ray irradiation. In the nine cases discussed fibrinogen was found to be high; no correlation

has been found so far with changes in the albumin and globulin pattern nor with clinical changes.

Wuhrmann and Wunderly (1947, pp. 130, 158, 163) have found that the E.S.R. depends in the first instance on fibrinogen; also on the globulins, where an increase of any single fraction may increase the rate; or there may be a simultaneous increase in several fractions. The accelerating effects on the E.S.R. of fibrinogen, euglobulin, pseudoglobulin, and albumin are in the ratio 100 : 20 : 2 : 1.5. Luetscher (1947), and also Malmros and Blix (1946) agree that, besides fibrinogen, a rise in any globulin fraction may cause an increased E.S.R.

In rheumatoid arthritis the E.S.R. is generally found to be increased due to higher fibrinogen and globulin values. Wuhrmann and Wunderly (1947, p. 238) found a marked persistence of a high E.S.R. in cases which were refractory to treatment.

In the present investigation no correlation between E.S.R. and changes in fibrinogen and globulin or with clinical improvement or deterioration has been found. It may be that the x-ray irradiation influences the E.S.R.; it is also possible that a continuation of a raised E.S.R. during a remission in rheumatoid arthritis indicates that the systemic disease is not burnt out in spite of a return in quantity to the normal range of the albumins and globulins, the question of quality remaining open.

Unfortunately it was not possible to increase the number of laboratory tests. For a more thorough investigation it would be necessary to take more frequent readings, including several before any treatment is initiated. The serum albumin-globulin patterns should be compared with those of rheumatoid arthritics undergoing other types of treatment (especially chrysotherapy and ultra-violet light), of cases of allergy (especially bronchial asthma and industrial dermatitis, in both of which x-ray therapy has been successfully used), of cases of hepatitis with icterus, of pregnancy, and of cases of disease (other than rheumatoid arthritis) which show a similar low albumin and high globulin pattern. It is possible that detailed quantitative methods will reveal significant differences, especially if electrophoretic values of fractions could be made, not in sporadic single readings, but as a series. When further discoveries allow qualitative investigations we shall probably be able to make a great step forward.

Summary and Conclusions

An investigation is reported on nine cases of rheumatoid arthritis treated with wide-field, soft x-ray irradiation.

In all nine cases the disease was advanced and had previously failed to respond to standard treatments. The cases were all apparently similar clinically (except for degree of severity), but low serum albumins and high globulins were found in six, and nearly normal values in the other three.

Following treatment the six cases responded favourably with clinical improvement and a return of the albumin-globulin pattern to normal. Of the remaining three cases, two showed no clinical improvement and unfavourable movements in the albumin-globulin pattern; the third (borderline case) improved belatedly and so far only for a short period, both clinically and in the protein pattern.

Functional liver tests in the six responding cases revealed no abnormality, but definite abnormality was found in the two non-responding cases and slight abnormality in the remaining case.

It is suggested that: (1) The serum albumin-globulin pattern is an unspecific but reliable indicator of the body's reactive state; (2) soft, wide-field x-ray irradiation can influence a pathological albumin-globulin pattern, at least in cases of rheumatoid arthritis; (3) a return to more normal albumin-globulin levels is followed by clinical improvement in rheumatoid arthritis; (4) a shift in the protein pattern in the right or wrong direction foreshadows clinical improvement or deterioration; (5) an adverse shift of the albumin-globulin pattern does not necessarily signal an imminent flare-up of the rheumatoid arthritis since such a shift may be caused by an intercurrent disease, without manifestation of a relapse in the rheumatoid arthritis.

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Le mécanisme Défensif du Corps Humain, Peut-il être Influencé par l'Irradiation Roentgenthérapie ?

RÉSUMÉ ET CONCLUSIONS

On rapporte sur les recherches dans neuf cas d'arthrite rhumatismale traitée par des rayons x mous sur un champ étendu.

Dans tous les neuf cas la maladie était avancée et elle n'avait pas cédé antérieurement aux traitements classiques. Tous les cas présentaient l'apparence clinique similaire (sauf en ce qui concerne le degré de sévérité), chez six malades toutefois on a trouvé de basses valeurs pour les albumines sériques et de hautes valeurs pour les globulines, tandis que chez les trois autres ces valeurs demeuraient presque normales.

Chez ces six malades le traitement donna des résultats favorables, comprenant une amélioration clinique et le rétablissement des valeurs normales de l'albumine et de la globuline. En ce qui concerne les trois autres malades, deux d'entre eux ne montrèrent aucune amélioration clinique et leur taux d'albumine et de globuline évolua d'une façon peu favorable ; le troisième (cas intermédiaire) fit un progrès tardif et, autant qu'on sache, de courte durée tant du point de vue clinique que sérique.

L'examen de la fonction hépatique ne revela rien d'anormal chez les six malades qui réagirent favorablement, mais une anomalie confirmée fut trouvée dans les deux cas réfractaires au traitement et on observa une légère anomalie chez le troisième.

On suggère que : (1) les valeurs sériques de la globuline et de l'albumine offrent une indication non spécifique mais sûre pour juger l'état réactif de l'organisme ; (2) l'irradiation étendue par des rayons x mous peut influencer les valeurs pathologiques de l'albumine et de la globuline, tout au moins dans des cas d'arthrite rhumatismale ; (3) un déplacement du tableau protéinique dans la bonne ou dans la mauvaise direction présume une amélioration ou une détérioration clinique ; (4) un déplacement défavorable des valeurs de l'albumine et de la globuline ne veut pas nécessairement dire qu'une aggravation de l'arthrite rhumatismale est imminente puis qu'un tel déplacement peut être causé par une maladie intercurrente, sans qu'une rechute de l'arthrite rhumatismale se manifeste.