Historical Documents
In Search of the Cure for Rheumatoid Disease

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A theory need not be correct; it need only work!
— John W. Campbell, Jr.
FOREWORD

The long and true history in the search for the cause and cure of Rheumatoid Diseases — numbering perhaps up to 150 different presenting symptoms — may never be known. Surely the work of Roger Wyburn-Mason will sound through coming ages. But what of all those others who’ve reasoned or serendipitously discovered interesting and similar clues? Either with or without Roger Wyburn-Mason’s hints?

And what of those hundreds, perhaps thousands, of dedicated physicians who want to help their suffering patients so much, that they are willing to brave the hostility and vendettas sure to be raised if they should try to help?

This booklet — a mere sample of what must lie out there in the physician-practitioner’s files — should be dedicated to all those who’ve discovered a medical truth, only to be shot down by either the establishment or the system within which the establishment operates.

PERRY A. CHAPDELAINE, SR., EDITOR
FACTS AND THEORIES
ABOUT RHEUMATOID ARTHRITIS
JACK M. BLOUNT, JR. M.D. — 1954

What do we know about arthritis? Actually very little. We only have some notions about its cause, and without a good understanding of the cause how can we treat it intelligently? Rheumatoid arthritis, contrary to the opinion of many, is not just a disease of the joints but is a disease of the whole body. It affects every tissue and every function including intellect, digestive and excretory systems, as well as nontangible things like ambition. What kind of a disease process could cause so many varied disturbances in the human body?

As has been intimated, its main physical symptoms are red, swollen and tender painful joints. These predominate the clinical picture. It has been shown that the pathogenesis behind these swollen joints is an acute inflammation of the connective tissues in and around the joint and tendon insertions. Doesn't it stand to reason that the same thing that causes the changes in these connective tissues would cause certain changes in other tissues also? What is it in the human body that causes such abnormal reaction? Diligent search has not revealed the true answer. But isn't it true that the changes conform well to the pattern of allergies or hypersensitive reaction to allergens or endotoxins? Is this why cortisone and ACTH have been proven beneficial in the treatment of those diseases? That is: Do these act as a super anti-histaminic or sensitizer?

In June 1954, a few days before my second attack of acute rheumatoid arthritis, I had had fleeting sore peristaltic pains across the abdomen many times during the day, and seeking relief by bowel movement would evacuate very little except mucus. Bowel movements were accompanied with much tensesmus. Not much attention was given this malady but several times the thought of amebic colitis crossed my mind. Later, after the arthritis developed and the symptoms of colon trouble persisted and became aggravated, more serious thought of amebic colitis was entertained. Being out of town at the time, laboratory studies of the stool were not available, but with the symptomatology there is no doubt in my mind that the abdominal trouble was amebic. I started myself on milibis and took it for eight days. The bowel trouble cleared up completely. The clearing of the arthritis followed except in the ankles which were constantly traumatized by ambulation.

What does this mean? Could it be possible that there is some connection between the amebic infections and arthritis? Doesn't it seem rational that the body might absorb enough toxins or be sufficiently sensitive to the presence of certain radicals of an amebic infection to cause an hypersensitive reaction in an individual manifested in the form of acute rheumatoid arthritis? This is only one case, I know, but I think the evidence is sufficiently strong that it warrants further investigation. Doctors through the decade have been looking for a focus of infection to incriminate. Could this be it?
Dear Doctor:  

When did the endocrines, particularly sex hormones, come into trial for osteoarthritis? I think it was about 1920, but I was only one year old then and my medical reading wasn’t very extensive. Endocrines just didn’t work. This weekend I came across an article, probably written by a publicity man, about the use of endocrines for the treatment of osteoarthritis. I read on a bit.

Quite obviously, I thought this could be some promotion by the third assistant professor of chiropractic in a six-month’s chiropractic school. I was getting ready for a good belly laugh, then I was suddenly brought up short.

The article cited Doctor Varon, Director of Endocrine Research at Baylor University Graduate School of Medicine. This brought up lots of thoughts. I used to be a medical school professor and I know you had better not come up with jackassical stunts like this unless you are pretty sure. You might end up being Doctor Harold Varon, sole proprietor of the Gunville service station. It takes great determination to lay your medical future on the line. I have done it a few times. You sweat blood.

I have seen a few x-rays and just as the doctor says, there was osteoarthritis and then there wasn’t. You know, I like the ways in which Doctor Varon wants to research this. He would like to have a great number of doctors try it under the conditions of practice. From the results of this practice trial, he will know the story very quickly. Fellows, this seems just the way that research should be done. If he is right about curing osteoarthritis, we should all get together and build a monument to him. If he is wrong, I have a job for him driving mules on my farm. To talk to him, you may call his office and the phone number is: (214) 824-8753.

Now, fellows, remember how many doctors there are in the United States? Probably Doctor Varon likes doctors just as well as I do, but the 73rd call when he wants to go to the pot or is hungry, becomes less charming. You might write him at 3814 Swiss Avenue, Dallas, TX 75204.

Viva la Professor.

There was a letter from my mother the other day. Mom is quite a woman. She freely admits to being sixty-one years of age. Since I am 57, she must have been four years old when she bore me. Unfortunately, I know how old she was when I was born. She is now pushing 96.

Always she has a story for me. This one, although old, is a good one. Our first politician was Christopher Columbus. You see, he didn’t know where he was going, he had no idea where he was when he got there, had not the slightest knowledge of where he had been when he got back, and it was all done on borrowed money.
Mom, you will never make it to be 100 putting out stories like that.

In Memphis, there is an internist named Archimedes A. Concon, M.D. His name isn't any worse than mine. My middle name is Shan, which my father gleefully informed me is a colloquial Chinese expression for ignorant. You see, you have a smart man and a dumb man (me) thinking together. I should assure you that all these thoughts are from Archimedes. You can reach him at 4939 Princeton Road, Memphis, TN 38117.

Archimedes is one of the small but select group that has pointed out to us that viral infections quite obviously, like bacterial, can be either fast or slow. Let's take an example from the bacterial field. An example of a fast bacterium is pneumonia. An example of the slow bacterium is leprosy. Archimedes and some others say that we haven't recognized the slow viruses. Many of the ill-defined, but numerous diseases may be due to a slow virus.

Some of them should respond to metronidazole. It was no sooner put out than tried. A whole series of two patients, one with lupus erythematosus and one with psoriasis were put on metronidazole. Both cleared up. Now, Doctor Concon is looking for a case of eczema and vitiligo.

Now, fellows, Archimedes needs help, not criticism. Probably, the theory of slow-acting virus diseases is quite right. It may be that we have a broad spectrum [virustat]. It is surely beginning to look like it now.

Let me think for you and you should pick all the holes you can pick in my thinking. For the last two months, I have been reading wildly on cancer. Believe me, I won't make you suffer through any of that. Let's talk about viruses and cancer.

In animals, there are some malignancies that completely satisfy the postulates of Koch. We can say that life is subject to invasion by viruses with resultant malignancies. We didn't say one word about man being subject to such an invasion because we don't know. It seems reasonable to suppose that he would be. Can viruses cause a tumor in man — I said tumor, not CA? Of course. What about a wart?

From now on 'coincidences' pop up thick and fast. The tumor most nearly proved to be viral in origin is Burkitt's sarcoma [lymphoma: Ed.]. This is not really of great significance. All the people in the world with Burkitt's sarcoma [lymphoma: Ed.] could conveniently stand in one square block of space. The significant thing is that the virus implicated is a member of the Herpes' family — DNA.

Much of the work we have been doing is with Herpes' virus. Every herpetic infection which we have treated with metronidazole has definitely responded.

The one that shakes me is infectious mononucleosis. facetiously, it has been called a self-limiting malignancy. Mono is about as close to being cancer as you can be and still not have malignant characteristics. It clears up in three to five days under metronidazole.
There is a great deal of similarity between leukemia and mono. Now, I don't know whether various forms of leukemia are caused by virus. At least a thousand men in this country working in the fields think very probably they are. Is the purported virus DNA or RNA? If it is RNA, we will do no good at all, or so I think.

Anyway, this is the job for almost all of us. If there are no results, it will be over in a matter of a month. Even negative information helps with cancer.

**Practice**  
*Practice Research, Inc.*  
A Non-Profit Corporation of Laurel, Mississippi  
PAUL WILLIAMSON, M.D.

Dear Doctor:  

September 1, 1976

We are now ready to announce a wide-spectrum virustatic agent. There never has been such a thing before in medicine. It is just metronidazole or plain old Flagyl®. You should be able to use it quite widely, thereby bringing under control many virus infections you have previously been unable to control.

Fellows, I really think this is equivalent to Fleming's discovery of penicillin. I still don't have any idea of the parameter in terms of viruses susceptible to metronidazole. We do know enough that we can tell you right now metronidazole will knock off at least fifteen diseases.

Three people worked on the majority of the development. They are James Rowland, D.O., of Kansas City; Archimedes Concon, M.D. of Memphis; and me. About two or three thousand more of you are taking an active part. Now, metronidazole will not touch RNA viruses. It appears to be effective in most of the DNA viruses.

Here is a similarity to the discovery of Penicillin: Metronidazole has been known for x-years. It has been used for Trichomonas vaginalis as an amoebacide. Doubtless, you think that penicillin was discovered in 1927 by Sir Alexander Fleming. Certainly it was. The mold was known before he was born. He did not have the first usage of Penicillin. If my information is correct, in 1908 a St. Joseph doctor was severely disciplined by the medical society for feeding pneumonia patients moldy bread. The mold on the bread was *Penicillium notatum*. He had the simple choice of stopping the investigation or stop practicing medicine.

Now let's discuss the carcinogenicity of metronidazole which is absolutely foolish. You see, I am intimately acquainted with metronidazole from the time of its first development in Europe. There was no hint of carcinogenicity. There still isn't. Then I went to South Africa, where Doctor Elsdon-Dew was just beginning his investigation of metronidazole on amoebiasis. Of course, Doctor Elsdon-Dew has given more metronidazole than anybody in the world. He says that the drug is of a low order of toxicity. I believe he knows more than a mouse experimenter with the FDA. I have seen him twice since then and his statement has not changed.
Two points are of some significance, and a third is of almost overwhelming significance. First, if it is so damn bad, why didn't the FDA take it off the market? Buy all you want. Second, we are using it to treat the very type of cancer that the mouse had. Very strange. This just doesn't stand to reason. Finally — and this is the overwhelming bit — there has been a big patent foofoooraw. It looks as if Searle was losing and they might want to kill the drug. Look it up, you can see. This isn't particularly apropos, but I offered to bet Marion Finkel, M.D., a high-up in the FDA, that by varying the conditions of the experiment we could make water carcinogenic. The FDA must stop these publicity campaigns. They must be able to prove something before they yack about it. The word 'carcinogenicity' is a terror word anyway.

Fellows, all you can do is not to take my word, not to take the FDA's word, or even Elsdon-Dew's. Just look and see. I have never seen a cancer even remotely related to metronidazole — I am talking about human cancer. I have seen quite a few cancers that give good signs of being cured by administration of the drug.

Now let's talk about what the drug will do. When it has worked in more than one-hundred cases we will say we are "positive." When it has worked in less than a hundred, we will call it 'probable'. If it looks as if the drug will work, but we have not had any chance to do more than preliminary investigations, we will call it "we will see".

Now we didn't start the original drug. It's first use, and its only one in viruses, was reprinted in the Lancet in 1964. [The year Prof. Roger Wyburn-Mason published A New Protozoan and finding Naegleria Ed.]. It spoke of it being effective in first-infection herpes. It surely is. This is a fairly rare disease. Why they didn't carry research further, I don't know. We started extensive research in about 1968.

About herpes simplex, we are positive. We have well over a thousand cases. There is a lot more herpes simplex, even semi-serious cases, than I knew.

Herpes zoster, we are positive. About four to five-hundred cases have been treated.

Genital herpes, we are positive. There are hundreds of cases.

There are a bunch of strange cases that appear to be herpes simplex but in unusual locations. For instance, we know of one that breaks out behind the knee and another that breaks out in the nares. Metronidazole works well. Keep in mind that the drug is virustatic, not virucidal. If the virus is not killed, there may be another outbreak in six months to a year. The second outbreak is healed as readily as the first.

About infectious mononucleosis, we are positive. There have been about one-hundred-fifty cases. There is an interesting thing about infectious mononucleosis. It is as near a blood malignancy as we see to spontaneously resolve itself. Apparently, the virus of infectious mononucleosis and leukemia is the same. They certainly look the same. It takes about six days to cure infectious mononucleosis.
Leukemia: everybody is afraid of Big Brother. This, to me is unbelievable. Leukemia has one hundred percent fatal prognosis unless metronidazole will save the patient. Still, a mouse possibly dies of the carcinogenicity of metronidazole. Probably this is not true. He dies of carcinogenicity from manipulation of the experiments. Which are you more interested in, people or mice? Reflect on this, will you? Let's don't let people die when we possibly have a way to save them.

Lymphomas: these are almost proven to be of herpetic virus origin. I don't know what result is forthcoming. We certainly haven't enough cases. Some of our work is going on in Africa. It surely looks good but there isn't any part of a hundred cases yet.

You see, we are out of space in Practice. In the next issue I will continue, and we still have two-thirds more diseases that we have started investigating or plan to do so. Now remember, this is a wide-spectrum virustatic agent. It works well. There never has been anything close to this in all of medicine in all time. Can you understand why Jim, Archie, and I are a little proud of this?

**Practice**

*Practice Research, Inc.*

A Non-Profit Corporation of Laurel, Mississippi

PAUL WILLIAMSON, M.D.

Dear Doctor:

October 1, 1976

Please remember that you have to write in if you want Practice. It is still free. The thing we are trying to do is get rid of the doctors who simply throw it away without reading. Repeated surveys have shown that Practice has the largest readership of any medical publication and has had for almost twenty years. Still, about thirty percent of you throw it away. With the expense of mailing, that amounts to a great deal.

All right. Let's go on with the wide-spectrum virustatic agent. We haven't nearly enough cases, but those that we have treated responded well. We really need a virus laboratory for this one. The Army has one near Leavenworth, Kansas, but we can't find it. I am telling you the truth. Anybody who lives near Leavenworth, find the address of the virus lab and the name of the boss, and let me know.

The adenoviruses: there are at least five diseases, and possibly more, and each one takes epidemic form. That is why we are interested in the Army lab. In addition to taking epidemic form, the only way you can positively diagnose adenovirus is with an adequate lab. By the way, here is a listing of the five diseases.

Acute Respiratory Disease, which is usually called a Cold, but actually it is not. Then there is the real killer, Pneumonia in children, Pharyngoconjunctivitis, Keratoconjunctivitis, and finally Febrile Pharyngitis. We have treated Acute Respiratory Disease and Febrile Pharyngitis with excellent results. There are still not enough cases to satisfy our requirements of a hundred.
There are 100,000 cases of smallpox per year around the world. Some of them certainly are in India. We have just gotten started on survey work through a personal friend that I have in India. I will let you know as soon as I know.

Screwball things keep showing up. For instance, I thought I knew what caused Bell's Palsy. I guess I didn’t because it seems to clear right up with metronidazole. We have about six or seven cases. A doctor in Utah wrote me about a man who had had severe pain in the jaw for over twenty years. Under Metronidazole, it promptly got well.

Here is a funny one: we live eighty miles from the State Health Department in Jackson. Of course, no man from the county really ever had anything right. You see, there seems to be a definite relationship between distance and erudition. We wrote the State Health Department about viral hepatitis. They did not answer the letter. Then I put it in Practice. A doctor in Massachusetts sent us the information we wished.

Now come the slow viruses. Oh, boy. Here we have to take a double-pronged attack. There are essentially two research programs.

We take diseases of unknown etiology and sort through them looking for typical manifestations of virus. Then we try them on the virustatic drug. Since we know exactly what the virustatic will do bacteriologically — which isn’t much — we assume that the diseases which respond must be virus. If they are DNA we expect the patient to get well. So far, they have.

Now this in itself is quite a leap upward for medicine. We are establishing the etiology in many diseases where the etiology has not been known. Then we cure the disease — or at least we did every one that is DNA virus. To me, it seems that we are bound to fail before long. We haven’t so far, but we haven’t gotten very far into the slow viruses. Slow viruses are slow work.

There is a club of about 2,500 members over the world. Nobody wants to join this club. To get in, you have to have positively diagnosed Lupus erythematosus. The club represents about twenty percent of the lupus victims known. I did not even know about it. They knew about us. We are almost to the point of proving that Lupus erythematosus is a slow virus. We have cures but not enough.

Mrs. Hull, the bullgoose of the club, talked with me quite a while about it, and agreed to write a short article for the club publication. I’ll bet we will have 1,500 or more cases to report to you within two months.

Here are some diseases that appear to have a viral etiology. We will check them as quickly as we can. Please, you help us check. It is so simple. Just give one tablet of metronidazole t.i.d. You will notice that the dosage is approved by the FDA. [The Rheumatoid Disease Foundation protocol is different: Ed.]

Dermatomyositis is an excellent possibility. Another possibility is scleroderma. Then there is melanoma of which we are not very sure. Hodgkin’s disease looks good. Paget’s disease is como se, come sa. Sarcoid possibly should respond. Alopecia aerata almost certainly will respond. These aren’t frequent diseases, as you know, but quite a few of them are fatal.
Of course you know as well as I do that viruses frequently enter the body through the eye. Look in some eye book and notice the number of 'etiology unknown' statements in it. Jim has just started on the eye. He had good results but not nearly enough cases. He is going to find an eye man in Kansas City to work with him.
The attached paper has been sent to a selected group of individuals for consideration, evaluation and investigation.

Perhaps someone in your group or organization has a special interest in the area of rheumatoid arthritis and will take the time to consider this paper.

The patients have graciously agreed to make themselves available on a reasonable basis for interview, evaluation, examination and investigation.

We are at your service.

"The philosophy of drug use in rheumatoid arthritis is not to obtain a cure . . ." (emphasis added). This remarkable statement (4) reveals the resignation and discouragement bordering on despair apparent in our approach to the management of many chronic "incurable" illnesses.

"I would now like to mention a few words about unproven methods of treatment — or quackery." This remarkable statement (5) introduces a discussion which includes the following comment about a reported cure for rheumatoid arthritis and, therefore, by association, equates the claim with quackery. "Recent claims that RA (rheumatoid arthritis) is a protozoal disease have come from Great Britain and cures are claimed after a course of treatment with clotrimazole, an anti-helminthic drug."

The first statement implies there is no hope and the second forbids it on threat of sanction by the medical community. Fortunately the philosophy of medicine embraces both hope and cure as desirable concepts. In our approach to illness there are available only three valid choices (barring our willingness to do absolutely nothing) in the order of their importance and priority:

1. prevention where possible;
2. cure where possible and where prevention has not been accomplished or is not yet possible;
3. palliation where prevention and cure have been accomplished or are not yet possible.

The fallacy and fantasy inherent in the imprecise concept of quackery deserve more than passing comment. The free use of such an imprecise term can impede medical process when it impugns by implication the sincerity, integrity and competence of those who would pursue unique solutions to "insoluble" problems. Quackery often seems to reside primarily in the eye of the beholder, for yesterday's approved medical therapy can quickly become today's quackery while former quackery becomes respected therapy.
Medicine in recent years has avoided much morbidity, mortality and human suffering when it:

1. replaced the ubiquitous tourniquet with direct pressure to control bleeding,
2. replaced the petroleum jellies, butters, oils and greases with clear cold water in the treatment of acute burns, and
3. insisted on early postpartum and post-surgery ambulation to avoid the complications of prolonged bed rest and inactivity.

We are proud of our medical progress and might not tolerate a “quack” who persisted in the former modes of therapy.

A few competent, conscientious, caring physicians may feel just a little heartsick as they read the following excerpts from A Guide To Health (3) which was written by Benjamin Colby and published in 1846:

1. On bleeding wounds:
   "The first object is to stop the bleeding. When an artery is cut, the blood is of a bright scarlet color, and gushes from the blood-vessel in a jet, with great force. The bleeding may be stopped with a pledget of lint rolled up and pressed directly upon the mouth of the artery. The next object is to cleanse the wound from all extraneous substances. The sides of the wound should then be placed together, and confined by narrow strips of sticking plaster. Over these strips should be placed a cushion of soft lint; and over the whole a bandage drawn agreeably tight, and making equal pressure."

2. On acute burns:
   "The best application that can be made to burns or scalds, when first done, is cold water. Take a cloth wet in cold water, and wrap several thicknesses round or lay on the part, to be wet as often as the pain returns."

3. On childbirth among the Indians:
   "Nature is their only midwife. Their labors are short, and accompanied with but little pain, and she returns in a few days to her usual employment; so that she knows nothing of those accidents or the weakness that arises from a month’s (bed) confinement in a warm room."

I agree that:
"Many of these quackery practices flourish because of ignorance. So, much more effort must be directed at educating the public and at the continuing education of physicians."(5)

This requires communication among individuals which hopefully will lead to the achievement of desirable common goals and this prompts me to offer, without apology, a final excerpt from the preface to the above-cited volume, A Guide To Health.(3)
"The only way to prevent quackery is to diffuse a knowledge of medicine among the people, and also to point out to them the proper course to pursue to prevent being sick. This I have made a feeble effort to do in this little work, reserving nothing for future emolument, for which I expect to be ridiculed by those it is designed to benefit, and persecuted by those whose craft is in danger; begging the pardon of the literati for entering the author's ranks with so few of the requisite qualifications, but asking no favors of the medical faculty, scientific as they may be; for if I have not succeeded in proving the system true, it cannot possibly come farther from the truth than their own".

RHEUMATOID ARTHRITIS

Rheumatoid arthritis is generally described in the texts and literature as a chronic, incurable, systemic illness presenting with diverse clinical and pathologic manifestations and a natural history of varying degrees of spontaneous remission and acute exacerbation.

Reference volumes (1, 2) are available which thoroughly explore the subject of rheumatoid arthritis and much recent medical literature (4-8, 14-119) is available on the antiquity, history, etiopathogenesis, clinical manifestations, pathology, complications, natural course, and treatment of the illness.

Research and theories on the etiopathogenesis (8, 15-26) of rheumatoid arthritis range from "A" (amoeba, autoimmunity, antigens) to "Z" (zymogens, zooids) while recommended, approved, and discredited therapies (4-8, 26, 28, 32, 37, 39-103, 113-117, 119) also explore the alphabet from "A" (aspirin, adrenocortico-steriods, acupuncture) to "Z" (zinc, "Zeppelin"*).

Of particular importance to this paper are the reported uses of the nitroimidazole class of compounds and their derivatives in the therapy of rheumatoid arthritis (5-8). Clotrimazol (6, 7) was reported, in 1976, as a clinical cure in twelve patients with active progressive rheumatoid arthritis after periods of treatment up to 12 weeks. In 1972, a report (8) was published of the treatment of 12 patients with active, refractory, progressive, rheumatoid arthritis using the nitroimidazole derivative "BT, 985. E. Merck AG". It is reported that all but one patient responded favorably to treatment lasting as long as 39 days. No reports have been found in the literature of any subsequent clinical trials, completed or in progress, designed to evaluate either if these reports.

This apparent disinterest is surprising considering the fact that "World Rheumatism Year — 1977" (9-11) will soon end and it would seem appropriate that maximum effort be expended to verify any promise of a major achievement in this year which has been dedicated worldwide to the problems of rheumatoid and allied disorders.

* Trademark for Instituto DeAngeli brand of prenalone.
The "National Arthritis Act of 1974-1975" (11, 13) places major, intense emphasis on the care and palliation of the unfortunate victims of illness while scarcely recognizing the desirability of prevention and cure: either of which would ultimately eliminate the need for the third alternative.

An exhaustive discussion on the evaluation of rheumatoid arthritis is presented in the above-cited reference texts and literature. The total evaluation includes estimates of disease activity and disability classifications with various approaches and systems presented; some consisting of more than 100 individual assessments.

During my association with the patients presented in this paper, I gradually developed a comprehensive but practical disability classification system (Table 1.) which, I felt, was particularly useful in chronic progressive disorders such as rheumatoid arthritis. My intent was to identify disability plateaus coincident with and recognizable by the patient in the natural course of his disability. Prolonged discussions with patients and their families and associates together with my observations served as a foundation on my attempt to establish a method of disability evaluation in which the patient's subjective self-evaluations, family input and my (hopefully) objective findings would show a reasonable degree of correlation.

Disability can be separated into two basic concepts:
1. Economic disability (loss of earnings, cost of care) and,
2. Medical disability (organic damage, Psychologic dysfunction).

At the risk of censure, I have tried to eliminate the economic disability factor from my classification system (preferring to leave it's cure to society as a whole) while endeavoring to reflect the physical "quality-of-life" represented by the patient's medical disability.

Recognizing the argument inherent in such phrases as "normal activities" and "ordinary daily activities", I chose to leave the philosophical definition of such phrases to future discussions.

**METRONIDAZOLE**

Metronidazole was first reported as useful for the treatment of Trichomonas Vaginalis in 1959, (120) and since that time has come into general use worldwide. It has been used freely in pregnant females and one study (121) reports on several hundred cases where the infants of such pregnancies were followed and examined with the conclusion that metronidazole posed no teratogenic or other toxic risk in humans. This is generally agreed with in a recognized pharmacology textbook (122).

A 1972 paper (123) reported an increase in certain tumors in tumor-prone mice as a result of high-level, lifetime feeding dosage. This study, together with papers on mutagenicity (125-130) and pressure from consumer advocate groups, prompted *The Medical Letter* (124) to advise, in 1975, that "Metronidazole should generally not be used in pregnant women."

Subsequent to the introduction of Metronidazole in 1959, many papers have
been presented on its pharmacokinetics and other medical uses (131-188) including such diverse disorders as amebiasis and Wilson's disease.

In an exhaustive search of the literature, I have found no report on the use of Metronidazole in the treatment of rheumatoid arthritis although some papers have come so close to it as to make one wonder why the association did not become absolutely apparent. For example: 1. A May 7, 1977, letter (131) published in The Lancet reports on the successful resolution of arthritis associated with Giardiasis (referred to in the letter as a "rheumatoid syndrome") when treated with Metronidazole (a number of these cases were reported with positive rheumatoid factors without a suggestion of possible application to the treatment of rheumatoid arthritis). 2. A paper (132) in February 1975 investigates the anti-inflammatory properties of Metronidazole and finds it effective in ulcers. No further studies were found in this regard.

Studies on the pharmacokinetics of Metronidazole (133-135, 138) show a rapid tissue diffusion with a serum half-life of 8.7 hours and a virtual return to base line levels after 48 hours.

Metronidazole has been administered in single doses as large as 15 grams (137-144) and in continuous courses of therapy for as long as 6 months (145-147) all without unmanageable toxicity or side effects.

**METRONIDAZOLE IN RHEUMATOID ARTHRITIS**

Metronidazole was used in the treatment of 2 cases of active, progressive, sero-positive, nodular rheumatoid arthritis in the following dose schedule: Week I — 250 mg. tid to determine patient tolerance to the drug; Week II through Week V — 500 mg. tid; Week VI — last week of therapy at a tapered dose of 250 mg. tid. Both patients tolerated the drug regimen with no complaints or evidence of toxicity or side-effects related to Metronidazole.

Each patient was given a complete physical exam, chest X-rays, and electrocardiogram. Each patient had a baseline laboratory series done prior to beginning treatment, weekly during treatment and periodically after completing the six-weeks Metronidazole therapy. These were extensive laboratory evaluations which included the following procedures: WBC, RBC, HGB, HCT, MCV, MCH, MCHC, WBC differential, platelet estimate, calcium, inorganic phosphorous, glucose, BUN, uric acid, cholesterol, total protein, albumin, globulin, A/G ratio, total bilirubin, alkaline phosphatase, LDH, SGOT, SGPT, GGTP, creatinine, BUN/creatinine ratio, iron, total iron binding capacity triglycerides, total lipids, sodium, potassium, chloride, total base, anti-nuclear antibody, C-reactive protein, HBS AG, RA latex, VDRL, T3 uptake, T4 RIA, T4 iodine, T7 index. Only the abnormal test results have been included in Table 2 (Case 1.) and Table 3 (Case 2.). The laboratory findings are discussed in the case reviews which follow.

**CASE 1**

This patient is a 47-year-old white female with an internal diagnosis of rheumatoid arthritis at age 36. She was given a poor "Class 5" disability rating (my system) when she began therapy with Metronidazole.
Despite her progressive disease she had been maintained on a treatment regimen of aspirin and weekly injections of ACTH and had never been exposed to gold, penicillamine, anti-malarials or anti-metabolites. ACTH was discontinued prior to starting Metronidazole. The patient was continued on aspirin. Supplemental iron plus therapeutic vitamins were added.

In addition to her arthritic disease, this patient used eye drops for marked dryness and eye irritation but had none of the related symptoms or findings of Sjogren's syndrome.

The patient's abnormal laboratory findings are shown in Table 2. It is interesting to note that with the exception of serology and anemia, the only abnormal finding was a transient slight elevation of LDH.

Following is a narration of this patient's progress under Metronidazole therapy. I feel this is pertinent because it closely parallels the progress of the patient in Case 2 although the patients presented with different degrees of severity, anatomic damage and areas of involvement.

Week 1: No apparent change in condition.

Week 2: Subjectively feels better with less pain but no apparent anatomic change.

Week 3: Complains of mild aches and pain only. Decrease in inflammatory swelling of wrists and ankles. Increasing voluntary activity.

Week 4: Minimal pain. Marked reduction in swelling of wrists, fingers, ankles. Rheumatoid nodules in elbows and on ulnar surfaces now becoming less prominent.

Week 5: No evidence of acute, active rheumatoid inflammatory joint swelling. Reduction in size of rheumatoid nodules is striking.

Week 6: Nodules less prominent. Some apparent correction in the ulnar deviation of the fingers.

Week 45: At the time of writing this paper this patient is in her 45th week since start of therapy. The rheumatoid nodules have resolved leaving only mild roughened areas in the tissue over the bony areas. The patient has changed from a "Class 5" disability to a "Class 2" disability (my system). She has resumed her usual physical activities and again does such tasks as needlework and setting her own hair. She now uses only an occasional aspirin dosage to relieve the discomforts attributed to her permanent arthritic changes.

**CASE 2**

This is a 68-year-old white male with active, progressive, sero-positive, nodular rheumatoid arthritis of at least 10 years duration. He presented with an associated Sjogren's syndrome with stable fibrocalcific changes in his lungs and active chronic hepatitis.

At the start of therapy, he was given a very poor "Class 6" disability classification (my system). I am certain that only his inner strength together with
### Table 2. Case 1.

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N* = Negative or within the range of normal
(-) = No test results
0.00 < 1.00 = Index below the lower limits of normal
0.00 > 1.00 = Index above the upper limits of normal
(+) = Positive or abnormal
the patient's insistence of a devoted wife saved him from a total bed-fast existence.

This patient, despite the severity of his disease, also denied prior treatment with anything other than aspirin, codeine for pain, and intermittent steroids. He was on only aspirin at the beginning of this therapy. Vitamins and iron were added.

The presenting problems included severe upper and lower extremity muscle atrophy, contractures of elbows and knees, inflamed and swollen joints, deformities of his hands and feet, and painful rheumatoid plantar nodules under the metatarsal heads which required that he split his shoe uppers and wear bunion pads on the soles of his feet to relieve some of the pain of walking.

I was extremely reluctant to offer this patient any hope. It was only after prolonged discussion regarding the permanent anatomic changes and damage which he had already suffered and we could not hope to improve that I agreed to begin therapy. This patient literally could not raise his hands with sufficient strength to feed himself.

My fears proved groundless. As the treatment progressed and the swelling and pain subsided I suggested that the patient should begin exercises to recover that muscular strength still possible. I was informed that those exercises were already voluntarily under way and included exercises to relieve the disabling contractures.

Now in the 24th week since beginning Metronidazole therapy, this patient has improved to a "Class 4" disability classification (my system). He now assists in his own personal care, drives his camper truck, is independently mobile, is free of nodules, pads and painful feet, and, with the improvements in his contractures, we like to tell him that he stands about 3 inches taller. Finally, it appears that this patient is lost to follow-up for a period of some months; he and his wife have driven to Florida to resume his favorite occupation — fishing.

The abnormal laboratory data for this patient are detailed in Table 3. The abnormal liver function studies were unexpected. It was starting to find the near normal results after one week of Metronidazole therapy and the consistently normal liver function studies after the second week of treatment. Also of note is the gradual improvement in the total iron binding capacity values.

DISCUSSION

It is almost axiomatic that the answer to any question or problem only multiplies the questions and problems. For my discussion, (provided my findings are verified) I will pose a few of those questions which come immediately to mind.

1. What is the mechanism of action of Metronidazole in rheumatoid arthritis?
2. What is the optimum treatment regimen?
3. How can Metronidazole aid in research on the etiopathogenesis of rheumatoid disease?
4. Is the recuperative power of the body the only reason for continued gradual improvement after stopping the Metronidazole?
5. What effect will Metronidazole have on other systemic collagen disorders such as systemic lupus erythematosus and juvenile rheumatoid arthritis?
6. What is the explanation for the rapid resolution of hepatitis in Case 2?
7. What is the explanation for the gradual improvement in anemia and total iron binding capacity?
8. Is the treatment effect due to Metronidazole or one of its metabolites?
9. How long will the patients remain in remission and how long must the patient remain in remission to accept the concept of a cure? As a corollary, will the etiopathogenesis reveal the possibility of a reacquired illness versus a relapse of an existing condition?
10. Should the medical and scientific community develop a worldwide research agency to correlate and evaluate diverse activities in each of the "unconquered" diseases as a practical matter versus the philosophical concepts embodied in activities such as "World Rheumatism Year — 1977"?

**TABLE 1: MEDICAL DISABILITY CLASSIFICATION**

Class 1. No limitation.
Class 2. Some limitation or decrease in normal activity regardless of psychic energy. Requires no assistance.
Class 3. Requires some assistance in ordinary daily activities. Still capable of nearly all personal self-care and grooming.
Class 4. Unable to perform detailed, prolonged or heavy physical activities. Requires daily self-care and grooming assistance.
Class 5. Ambulatory without assistance. Performs light uncomplicated tasks. Other activity limited to assisted personal care and grooming.
Class 6. Ambulatory with assistance only. Minimum self-care ability.
Class 7. Bedfast or wheel-chair-fast. Self-care limited to caring activities.

**REFERENCES**

NOTE: In an attempt to make the references more usable, they are listed according to KEY WORDS where applicable to the present paper.

**BOOKS**

RHEUMATOID ARTHRITIS


METRONIDAZOLE

23
I refer to the paper by Dr. B.D. Williams and his colleagues from the Royal Postgraduate Medical School, in the Journal of July 28th, 1979, page 235, describing a case with a severe exacerbation of the symptoms of rheumatoid arthritis soon after injection of gold thiomolate, in which they also draw attention to this as a not uncommon phenomenon, the pathogenesis of which they state is not known. However, they fail to see the significance of their observation. I would like to draw their attention to the fact that gold injections were used extensively in the treatment of tuberculosis before the discovery of specific drugs against the causative organism. They were sometimes effective in killing the tubercle bacillus and were shown to be active in vitro against a whole series of organisms, including treponema pallidum. Have the authors never heard of an Herxheimer reaction? This consists of an exacerbation of the symptoms of a disease when a drug which kills the causative organism is administered. It never occurs in bacterial diseases. It was first described by Herxheimer in the treatment of syphilis by organic arsenicals, which kill the treponema pallidum. It also occurs in other diseases in similar circumstances, such as when diethylcarbamazine, which kills filaria, is used in treating filariasis. The reaction that they describe when gold is given to cases of rheumatoid disease is a typical Herxheimer reaction and points to the organismal or infective causation of rheumatoid factor and specific organ auto-antibodies, which appear in the plasma are a response to this infection, just as occurs in many other infections, especially protozoal, and which disappears with successful treatment of the disease(1). The resultant auto-antibodies may play a part in causing some of the disturbances in rheumatoid disease.

If Dr. Williams and his colleagues would care to consult my recently published monograph(1) on this disease they will find I was able to recover from all the tissues of all patients with this disease a free-living amoeba of the Naegleria genus, by using the property of thermotropism possessed by many parasites of warm-blooded animals, including the free-living amoebae. These could be cultured in the laboratory and the effect of various substances on the organism tested. It was found that it could be killed by metallic copper and copper salts in minute traces, by organic gold compounds, by dilute solutions of bile acids, pentamidine, emetine and dehydroemetine, by clotrimazole and levamisole, both of which contain antiprotozoal imidazole groups, and in particular by 5-nitro-imidazole compounds, such as metronidazole, tinidazole, ornidazole and nifurazol, all of which have a spectrum of antiprotozoal, including anti-free-living amoebic, activity. When any of these substances were used in the treatment of active rheumatoid disease, they either caused a fairly rapid disappearance of disease activity or a typical Herxheimer reaction, that is an exaggeration of the symptoms of rheumatoid arthritis, exactly like that described by Dr. Williams and his colleagues, and usually followed by improvement and finally disappearance of symptoms and signs of inflammatory activity, sometimes, after multiple doses. They prove that rheumatoid arthritis or preferably rheumatoid disease is an infection with an organism which is affected by gold salts among other substances. Hence the occasional cure or
halting of the progress of the disease by gold treatment. The use of gold with its very toxic reactions can be dispensed with by simply using one of the 5-nitroimidazole antiamoebic compounds, such as metronidazole, which are innocuous.

Reference

The Doubtful Value of Cross-over Trials
PROFESSOR ROGER WYBURN-MASON

Sir,

Once again your Leading Article (September 8th. p. 511) is advocating the sacred cow of cross-over trials of drugs, so essential to statisticians and without which neither the F.D.A. in U.S.A. or the Committee of the Safety of Medicines in this country will deign to look at the treatment possibilities of a new drug. Just how misleading may such trials be? I recall a paper by a former student of mine in your journal soon after cortisone became available. It concerned the treatment of asthma with this hormone, using such cross-over trial, which received the accolade of a leading article in the same issue pointing out the excellence of the scientific method used in this model trial. What was the startling conclusion reached in the paper? That cortisone is useless in the treatment of asthma, whereas now it is the standard treatment! One of the phenomena which make such trials useless is the occurrence of the Herxheimer reaction, when drugs which kill the causative organism of a disease are administered to a patient with the disease. This phenomenon has been largely forgotten. It was first described by Herxheimer early this century after Ehrlich introduced organic arsenicals which kill spirochaetes for the treatment of syphilis. It consists of a sudden aggravation of the symptoms of the disease a varying time after the administration of the drug. This phenomenon may last for an uncertain period before dying down and is due to the drug killing the organisms in the tissues and liberating toxic inflammatory substances from their dying bodies. It proved fatal in some patients. The same phenomenon occurs in other diseases, but never in those due to bacteria. Thus, the administration to cases of filariasis of diethylcarbamazine, which kills filaria, may produce a similar temporary exacerbation of symptoms before finally benefitting the patient. A recent paper recounts the same phenomenon after administering gold salts to cases of rheumatoid disease. Gold salts kill various organisms including the tubercle bacillus and amoebae, suggesting the possibility that the latter may be the organismal cause of rheumatoid arthritis. If a cross-over trial had been used to evaluate the efficacy of organic arsenicals, diethylcarbamazine or gold salts in the treatment of these various diseases, a completely false idea of their value would be obtained. Too much reliance on cross-over trials is accorded them and they may be misleading. It is time common sense and above all clinical acumen and knowledge are used in addition to this apparent sine qua non in ascertaining the value of drugs, which cannot be done by statisticians alone. Their stranglehold on drug development should be realized.

R. Wyburn-Mason
References

The Fundamental Mechanism of Inflammation in Mammals and Man

**ROGER WYBURN-MASON, M.A., M.D., SC.D. (CAMBRIDGE), M.R.C.P. (LONDON)**

Royal Marsden Hospital, London, England.
Royal College of Surgeons of England, London

Abstract

Though large numbers of so-called ant-inflammatory drugs exist, none are completely effective in inhibiting the inflammation of rheumatoid disease and all may produce undesirable side-effects. To understand the reason for their inability to combat inflammatory changes consideration was given to past and new knowledge adduced by the author on the mechanism of inflammation in animals and man in particular the role played by the efferent nerve fibers in the posterior nerve roots. It was concluded that inflammation only occurs in tissues with an intact posterior nerve root supply, in particular the unmyelinated C fibers. It does not occur in the lens or in malignant tissue which contain no such fibers. It was concluded that inflammation was dependant on liberation of a neurohormone from the nerve endings in the peripheral tissues. Liberation of prostaglandins and histamine are secondary effects.

Introduction

It is now well known that histamine and prostaglandins are liberated in areas of inflammation in mammals. Most non-steroid anti-inflammatory drugs consist of either antihistamines or drugs with antiprostaglandin properties. At a recent count about 90 different types of nonsteroid anti-inflammatory drugs are or have been available for the treatment of the inflammation of rheumatoid arthritis. What is the necessity for such a multiplicity of these? The obvious answer is that they are all ineffective in completely inhibiting the inflammation and pain or their side effects are unpleasant or so dangerous as sometimes to be fatal. Corticosteroids have their own special dangerous side-effects. Yet manufacturers continue to produce more and more of these unsatisfactory drugs and a new one appears to be launched with great publicity and claims for its superiority almost every month. It seems that the mechanism of inflammation is not understood fully.
Observations

In order to understand the reasons for the failure of present so-called anti-inflammatory drugs to completely prevent inflammation in sufferers from rheumatoid arthritis it is necessary to consider the following observations about the nature of inflammation.

1. Deep or slow pain is conducted by the unmyelinated C fibers of the mixed peripheral nerves having their neurones in the posterior root ganglia. They originate in the skin and other tissues as well as the viscera. When irritated, they can transmit impulses in both prodromic and antidromic directions. Prodromic impulses produce the sensation of slow pain by conduction of impulses along the branch axons of the posterior root ganglia cells into the cord and thence to the brain. Antidromic impulses pass to the blood vessels and other structures in the region of the peripheral origin of the nerve fibers causing an increase in the blood supply, heat and oedema in these situations1,2, as occurs when the distal end of a freshly cut sensory nerve is stimulated in both man and mammals. My late chief, Sir Thomas Lewis, in his classical monograph3 showed that a mild local noxious stimulus to intact skin resulted in the “triple response.” This consists of a local area of capillary vasodilatation surrounded by one where the fluid contents of the blood have leaked out through the increasingly permeable capillary walls and this again by an area of local arteriolar vasodilation or “flare.” These are the fundamental changes of inflammation in miniature. The ease with which this response is induced varies with the subject’s emotional state and the presence or not of neurological or mental disease (tache cerebrale), itself indicating the importance of centrifugal nervous impulses in the modification of the “triple response.” Lewis showed that experimental section of the posterior nerve root supply to the affected area and its subsequent degeneration modified the “triple response” by abolishing the “flare” and it can be assumed that the same modification occurs in a full-blown inflammatory response to a stimulus by “antidromic” posterior nerve root impulses.

2. The writer extended these findings by recalling that in a limb affected by causalgia as a result of damage to the sensory fibers in the median or sciatic nerves a mild stimulus, which produces little or no observable reaction in the normal skin of the patient other than the triple response, may induce a severe and grossly excessive inflammatory reaction in the painful parts affected by the causalgia3,6,7,8. Furthermore, the inflammatory change so produced by a mild noxious stimulus, which in normal skin shows no obvious change or a minimal triple response and rapidly returns to normal, persists in the causalgic region and even progresses to ulceration or cellulitis without any attempt at healing. Again, water which is only warm and in no way painful in normal areas of skin may cause excessive inflammation and vesiculation in the painful areas, while mustard plaster applied to the affected skin blisters it more readily than in normal areas6.

3. In contrast, in cases of complete section of the sciatic nerve in the thigh, any neurological textbook records that the anaesthetic areas in the foot are liable to
develop painless so-called trophic sores or perforating ulcers, that is areas of necrosis NOT INFLAMMATION of the skin and underlying tissues, which show no attempt at healing or regeneration. The same applies to the anaesthetic areas of the hand in cases of syringomyelia, of the feet in tabes dorsalis and the peripheries of the limbs in leprosy. Common to the last three is destruction of the sensory nerve fibers to the affected areas. These trophic lesions have been wrongly attributed to neglected injury in the anaesthetic areas resulting in inflammation. Such an explanation is untenable, since, if this were correct, the trophic lesions should consist of inflammation, whereas they are areas of necrosis. The writer showed that, if a drop of mustard oil was applied to the normal skin in any of the above conditions, it produced typical transient painful inflammation, but, if applied to the anaesthetic areas in the region of the trophic necrotic sores, it did not cause pain, a triple response or inflammation, but a further area of painless necrosis with no attempt at healing. The same is true of experimental sciatic nerve section in dogs.

4. Eczema or dermatitis is an inflammation of the skin. It is well recognised that emotional upset involving increased nervous activity exaggerates the condition.

5. The lens, which is the only living organ in the body which has no nerve supply, is never subject to inflammation after injury.

6. The writer showed that malignant tumors have no motor or sensory nerve supply (other than those of the invaded tissue). Trauma or the application of drugs which in normal tissues cause inflammation, such as nitrogen mustard when applied to malignant tissue, do not induce pain or inflammation, but necrosis, hence the use of such drugs in the treatment of malignancies.

7. Local anaesthetics, such as cocaine, procaine and related substances, have been shown to be anti-inflammatory and lessen pain when applied to cases of conjunctivitis and rheumatoid arthritis. In this connection the writer had under his care two male monozygotic twins, aged 25 years, who both developed rheumatoid arthritis at the same time and of the same severity and became progressively worse in spite of identical standard treatment with the same anti-inflammatory drugs. One brother suddenly began to make a dramatic improvement in his condition with disappearance of all clinical evidence of active inflammation for no obvious reason. However, the sedimentation rate remained high and the pre-existing anaemia persisted. After persistent close questioning he admitted that he had started sniffing cocaine and was now an addict. His brother’s condition continued to deteriorate. This indicates that suppression of nervous impulses inhibits the inflammatory process.

Conclusion

These collected findings show that the pain and inflammatory response to injury, drugs or a local infection and the healing process depends on an intact efferent posterior nerve root supply and is primarily reflexly neurogenically produced with the liberation of neurohormones at the peripheral nerve endings. Liberation of prostaglandins and histamine is of only secondary importance. Inflammation does not occur in response to injury in a completely denervated
area or organ, but only necrosis and a failure to heal. On the contrary, in painful areas, the inflammatory response to injury is excessive. These findings accord with the role played by intact posterior nerve root fibers in the regeneration of the distal ends of severed limbs in amphibia. Section of a single sensory nerve root, for example the trigeminal or a spinal nerve, does not cause complete denervation of the corresponding tissue, since there is over-lapping from neighbouring sensory nerve roots. Hence, the incompletely denervated areas are not so liable to necrosis in response to trauma as they would be if the anaesthesia was complete. Necrotic areas do occur in the trigeminal distribution in some cases of trigeminal root section.

The ideal anti-inflammatory drug would be one with an anaesthetic effect on unmyelinated C fibers, but would not be habit-inducing. Pharmaceutical firms would be wiser to spend their efforts in some other direction than in producing even more anti-prostaglandins, but in any case the reason for the inflammation in rheumatoid arthritis should first be removed, but that is a separate subject.  

References

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Dear Dr. Wyburn-Mason:
RE: 6272-THE NEUROGENIC NATURE OF INFLAMMATION AND THE EXISTENCE OF TROPHIC NERVES IN MAMMALS AND MAN.

Your manuscript has been read with great deal of interest by our editor, but I regret to inform you that we have not been able to find a place for it in the American Journal of Medicine.

We are, therefore, returning it to you.

Sincerely yours,
Arthur J. Antenucci, M.D. Editor

Referee Comments

I think the author could rewrite this paper in a more concise way. If he would stick to his basic hypothesis in the data for and against the role of efferent neural function and information, I would find it an interesting and provocative paper. Others might well then use this as the basis for further experimentation.

This paper is unsuitable for publication in its present form.

The basic hypothesis that the author puts forth, that is, that the inflammatory response to injury and the subsequent healing process is dependent on an intact efferent nerve supply is of interest. In addition, the author's examples, chosen from clinical observations in experimental animals, seems to substantiate this hypothesis. However the author goes way beyond this in his statements.

For example, on page 7 in the first part of the discussion the author makes the statement that the inflammatory response are "primarily neurogenically produced with the liberation of neurohormones at the peripheral unmyelinated nerve endings." He really has no evidence that SP (substance P) is liberated at the peripheral nerve endings by stimulation. Furthermore he then talks about prostaglandins in histamine for the first time in this paper again with no direct evidence that they are involved at all in the process. Thus this part of the discussion, I think, is inappropriate.

On page 8 the author finishes with the statement, "Such a finding points to the fundamental uselessness of the present dozens of anti-inflammatory drugs produced for the treatment of arthritis." This statement coming quite out of the blue is very hard to digest. As a matter of fact, I don't quite understand what the basis is for why the author makes this statement. I don't think its in any way essential to prove or disprove his basic hypothesis.

Finally, there are aspects of this paper which make it difficult to read in terms
of basic interest. I will just pick one or two examples. On page three in the second paragraph, referring to unmyelinated C fibers, the author makes the statement, "They originate in the skin, bones, joints, and all other tissues as well as all of viscera passing through the autonomic ganglia directly." I have a great deal of difficulty understanding that particular sentence.

The Neurogenic Nature of Inflammation and the Existence of Trophic Nerves in Mammals and Man

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Summary and Conclusion
1. Though accepted by early neurologists the existence of trophic nerves has remained in doubt. Moreover, the exact nature of inflammation is not fully understood. With the discovery of the peptide neurohormone substance P (SP) liberated peripherally from sensory unmyelinated C fibers by local noxious stimuli and by antidromic impulses the situation is clearer. This paper shows that trophic nerves certainly exist in the sensory nerve roots and activity in them is responsible for inflammation and recovery from injury.
2. This is shown by the fact that inflammation does not occur in response to injury in tissues, such as the lens of malignant tumours, devoid of nerve supply.
3. In limbs in which the peripheral nerves are damaged, but not sectioned, the tissues supplied exhibit causalgia and an excessive proneness to inflammation in response to noxious stimuli, whereas when the nerves are completely sectioned noxious stimuli to the denervated tissues cause necrosis and no tendency to healing.

KEY WORDS: NERVES, TROPHIC INFLAMMATION, NEUROGENIC.

Introduction

That the nutrition of the elements in mammals and man is largely under the influence of the nervous system cannot be doubted, since damage to the mixed peripheral nerves leads to nutritional disturbance of the tissues supplied by the affected nerves. Whether the influence is exerted through special "trophic nerves" or through the sensory or autonomic nerves has been discussed. The distinguished French neurological school of the middle of the last century, such as Charcot and Trousseau, had no doubt that such special nerves existed, though they were unsure of their pathways. They did not exist in the motor nerve roots of the central nervous system and the idea that they were present in the dorsal or sensory roots and conducted antidromic impulses seemed to contradict Bell's law. Moreover, complete removal of the autonomic nervous system can be undertaken without the production of trophic lesions. Consequently the idea
that special trophic nerves existed gradually fell into decline in the first decade of this century. Nor was it suggested that nerve fibre activity was responsible for inflammation and recovery from it after injury. No major work on this subject was undertaken this century other than that described in the author’s monograph.

Deep or slow pain is conducted by the unmyelinated C fibres of the mixed peripheral nerves having their neurones in the posterior nerve root ganglia. They originate in the skin, bones, joints and all other tissues as well as the visera passing through the autonomic ganglia directly. When irritated, they can transmit impulses in both prodromic and antidromic directions. Prodromic impulses produce the sensation of slow pain by conduction of impulses along the branch axons of the posterior root ganglia cells into the dorsal horn of the cord and thence to the brain. Antidromic impulses pass to the blood vessels and other structures in the region of the peripheral origin of these nerve fibres.

Lewis, in his classical monograph, showed that a mild local noxious stimulus to intact skin results in the “triple response”. This consists of a local area of capillary vasodilatation surrounded by one where the fluid and cell contents of the blood have leaked out through the increased permeability of the capillary walls and this again by an area of local arteriolar vasodilatation and hotness or “flare”. These are the fundamental changes of inflammation in miniature. The ease with which the response is induced varies with the subject’s emotional state and the presence or not of neurological or mental disease (tache cerebral), itself indicating the importance of centrifugal nervous impulses in the modification of the “triple response” to stimuli.

Jancso showed that, if the saphenous nerve is sectioned in rats and soon afterwards a chemical irritant is applied to the area of denervated skin the latter responds normally to chemical irritants and becomes inflamed. If, however, the nerve is allowed time to degenerate and the inflammatory agent is applied to the denervated area no inflammation or flare result, showing that the inflammatory reaction in the skin depends on the intact function of the pain receptors and nerves, but the “flare” of the inflammatory reaction can be prevented by local anaesthesia. The same phenomena were seen in men. The author interpreted these results as indicating that the inflammatory reaction is neurogenic in nature and appears to be due to liberation of a “neurohormon” from the sensory nerve endings or pain receptors in the tissues and not to antidromic impulses. Release of the peripheral “[n]eurohormon” can be elicited not only by direct orthodromic stimulation of pain receptors with pain-producing chemical substances, but also antidromically by electrical stimulation of sensory nerves. Hokfelt et al., Iversen and Iversen and Burnstock reviewed the results of the rapidly advancing immuno-histochemical techniques as applied to numerous peptide-containing neurones in the brain, cord and peripheral nerves. This technique has shown the presence of a number of peptide-containing neuro-transmitters, of which the best-known appears to be the immunoreactive substance P (SP) found
in many cell groups in the central nervous system, in primary sensory neurones in the dorsal root ganglia, in sensory neurones in the vagus nerve and autonomic ganglia, in taste buds and in intestinal neurones. It appears to be produced in some of the ganglion cells of the dorsal nerve roots and be transported both peripherally and to the dorsal horn of the cord. Only some 20 per cent of dorsal neurones contain it and these have small probably unmyelinated or thinly myelinated axons. It is found in sensory peripheral nerve endings, where it seems to be located mainly in so-called large granular vesicles in the unmyelinated C fibres in the skin, which are those concerned in the transmission of pain. SP appears to be the afferent pain transmitter distally. It is also liberated peripherally producing vasodilatation and inflammation by antidromic stimulation of sensory nerve fibres. It possibly serves as a neurotransmitter in the central branches of the dorsal root ganglia terminating in the dorsal horn of the spinal cord. Within the central nervous system it also appears to act as a neurotransmitter particularly in the substantia nigra. SP seems evidently to be the same substance as the neurohumor of Jansco. If injected into the skin, it causes intense pain and inflammation.

Experimental methods and observations

A. Anatomical and pathological considerations

The lens of the eye in mammals and man is the only living organ in the body which has no nerve supply and when injected does not become inflamed, but opaque and disrupted. Moreover, the writer\(^9\) showed that all malignant tumors have no motor or sensory nerve supply (other than that of the invaded tissue). Trauma or the application of drugs which in normal tissues causes inflammation, for example nitrogen mustard, when applied to malignant tissue do not induce pain or inflammation, but necrosis. Hence the use of such drugs in the treatment of malignancy. Such observations suggest a nerve supply may be necessary for the development of inflammation in response to trauma.

B. Clinical considerations

1. The writer\(^1\) showed that in a limb affected by causalgia as a result of damage to but not section of the sensory fibres in the median or sciatic nerves a mild stimulus, which produces little or no observable reaction in the normal skin of the patient other than the triple response, may induce a severe and grossly excessive inflammatory reaction in the painful parts affected by the causalgia. Furthermore, the inflammatory change so produced by a mild noxious stimulus, which in normal skin causes no obvious change or a minimal triple response which rapidly disappears, persists in the causalgic region and even progresses to ulceration or cellulitis without any attempt at healing. Again, water which is only warm and in no way painful in normal areas of skin may cause excessive inflammation and vesiculation in the painful areas, while a mustard plaster applied to the affected skin blisters it more readily than in normal areas.

2. In contrast, in cases of complete section of the sciatic nerve in the thigh any neurological textbook records that the anaesthetic areas in the foot are liable to
develop painless so-called “trophic sores” or perforating ulcers often involving bone, that is areas of NECROSIS NOT INFLAMMATION of skin and underlying tissues, which show no attempt at healing or regeneration. The same applies to the anaesthetic areas of the hand in cases of syringomyelia, of the feet in tabes dorsalis and the peripheries of the limbs in leprosy. Common to these is destruction of the sensory nerve fibres to the affected areas. These trophic lesions have been wrongly attributed to neglected injury in the anaesthetic areas resulting in inflammatory destruction. Such an explanation is untenable, since, if this were correct, the trophic lesions should consist of inflammation, whereas they are areas of necrosis. The writer showed in three cases of complete section of the sciatic nerve that if a drop of 5 per cent mustard oil was applied to the normal skin it produced a triple response or typical transient painful inflammation, but, if applied to the anaesthetic areas in the region of the trophic necrotic sores, it did not cause pain, a triple response or inflammation, but further area of painless necrosis with no attempt at healing. Biopsy of this area and staining with haematoxylin and eosin showed no inflammatory phenomena, but only a mixture of dead cells and no nerve fibres with supravital methylene blue stain. The same is true after experimental sciatic nerve section in dogs. The writer obtained similar results in applying 5 per cent mustard oil near the anaesthetic trophic sores of the foot in two cases of tabes dorsalis and one of leprosy of the feet.

Discussion

These collected findings show that the inflammatory response to injury, drugs or a local infection and the following healing process in a tissue depend on an intact efferent dorsal nerve root supply and are primarily neurogenically produced with the liberation of a neurohormone (SP) at the peripheral unmyelinated nerve endings. Liberation of prostaglandins and histamine is of only secondary importance in producing inflammation. Inflammation does not occur in response to injury in a completely denervated area or organ, but only necrosis and a failure to heal because of failure to liberate SP in these areas. On the contrary in painful causalgic areas the inflammatory response to injury is excessive presumably due to an excessive liberation of SP. These findings accord with the role played by intact dorsal nerve root fibres in the regeneration of the distal ends of severed limbs or tail of amphibia. Section of a single sensory nerve root, for example the trigeminal or spinal nerve, does not cause complete denervation of the corresponding tissue, since there is overlapping from neighbouring sensory nerve root areas. Hence, the incompletely denervated areas are not so liable to necrosis in response to trauma as they would be if the anaesthesia were complete.

Necrotic areas do occur in the trigeminal distribution in some cases of trigeminal root section and the eye and gums may become necrotic. Such observations prove the existence of the once generally recognized, but now much doubted, trophic nerves producing peripheral inflammation and tissue regeneration in response to a noxious peripheral stimulus. Such a finding points
to the fundamental uselessness of the present dozens of anti-inflammatory drugs produced for the treatment of arthritis.

References.