particularly. I have carried out the operation in a few of these rheumatoid joints, removing as much as possible of the synovial membrane, the results being surprisingly good. The most remarkable feature is the development afterwards of a new synovial sac.

Patellectomy.—Brooke has shown how well patients can manage without a patella, and for those individuals with ankylosis of the patella to the femur I do not hesitate to remove it.

Osteotomy, particularly in ankylosis with deformity of the wrist-, hip-, knee-, and foot-joints, is a most valuable and simple procedure, the positions obtained being those already discussed. In most cases the site of osteotomy is at the old joint line, but for hip deformities it is intertrochanteric. If the ankylosis of the hip is fibrous then the bifurcation type of osteotomy is done, with displacement of the shaft beneath the acetabulum as devised by McMurray.

Arthroplasty has its greatest sphere of usefulness in non-weight-bearing joints such as the temporo-mandibular and elbow. The best results are obtained in cases previously having bony ankylosis. It is very important to remove an ample amount of intervening bone. For the hip-joint, where it would often be desirable to obtain free movement, particularly in bilateral ankylosis, the successes are not very frequent. For the distressing cases of spondylose rhizomélisque, in which both hips and spine are ankylosed, it is worth making a good effort to obtain at least one movable hip. The method recently described by Girdlestone of removing the entire head and neck of the femur offers great encouragement in this direction.

Arthrodesis.—In a disease that tends to produce ankylosis, arthrodesis is not commonly required. In the wrist and foot, however, painful fibrous ankylosis, with or without deformity, may have to be dealt with by this fixation operation. Subastragaloid arthrodesis may enable a patient to walk who is otherwise crippled by pain, and for distressing multiple claw-toe deformities Lambrinudi's method of multiple interphalangeal arthrodesis gives most remarkable results, and to the patient pleasing relief.

J. Touati (*Thèse Paris*, 1938, No. 121), who records six cases in patients aged from 22 to 63, illustrates the rarity of osteoperiostitis in the enteric fevers by drawing attention to the fact that only four cases were encountered in a series of 1,600 typhoid patients. The condition is most frequent in young subjects, its incidence being highest under 25, and it is very rare above the age of 35, although it is occasionally found in elderly persons. The complication is most commonly met with in atypical forms of the fever in individuals who have not acquired a high degree of immunity against the specific bacillus and are apt to show a low degree of agglutination. It is due to persistence in the bone marrow of the bacillus, which gives rise to circumscribed lesions and behaves like a pyogenic organism. The osteo-periostitis may appear at an early or late stage of the fever, but in the great majority of cases it develops six to eight weeks after the onset, and sometimes not till several years later. The commonest organism is *Bact. typhosum*. *Bact. paratyphosum B* comes next, and *Bact. paratyphosum A* is hardly ever found. In some cases the typhoid or paratyphoid organism may disappear and be replaced by secondary invaders, such as the streptococcus, staphylococcus, pneumococcus, or *B. coli*, in which case the prognosis is usually grave. As a rule, however, the outlook is favourable, and in spite of the slow course and frequency of relapse complete recovery takes place. In non-suppurative forms vaccine treatment alone is required. In some acute suppurative forms operation may suffice, but usually both vaccine and operation are employed.

EFFECT OF SPONTANEOUS JAUNDICE ON RHEUMATOID (ATROPHIC) ARTHRITIS*

ATTEMPTS TO REPRODUCE THE PHENOMENON

BY

PHILIP S. HENCH, M.D.

*Division of Medicine, The Mayo Clinic, Rochester,
Minnesota*

When patients with rheumatoid (atrophic, chronic infectious) arthritis or with primary fibrositis become definitely jaundiced a notable event usually occurs: their rheumatic symptoms are rapidly, markedly, and generally completely alleviated for some weeks or months. My first observations on this phenomenon were reported in 1933 and later (Hench, 1933a, 1933b, 1934, 1935). This phenomenon was unmentioned in the modern literature on rheumatic diseases, but was casually noted by Still in 1897, by Wishart in 1903, and in three recent discussions, not on arthritis but on cinchophen toxicity (Parsons and Harding, 1932a, 1932b; Grigg and Jacobsen, 1933). More recently further observations on the phenomenon were reported by Sidel and Abrams (1934), and by Borman (1936). Heretofore the possible significance of the phenomenon has not been fully appreciated.

Recently I presented further observations (Hench, 1937, 1938a, 1938b) on two new groups of cases: (1) studies on thirty-one additional rheumatic patients who experienced the phenomenon; and (2), of equal importance, studies on four patients with rheumatoid arthritis and on nine patients with other types of articular and neuritic complaints who were *not* relieved of symptoms coincident with jaundice. These observations will be summarized briefly.

Effect of Spontaneous Jaundice

Symptomatic remissions lasting from five to ninety-two (average 19.5) weeks occurred in nineteen cases of rheumatoid arthritis (average 5.5 years' duration) in which intrahepatic or obstructive jaundice lasted an average of nine weeks. Remissions continuing for four to 104 weeks occurred in nine cases of fibrositis in which the jaundice lasted an average of 5.6 weeks. Two patients with lumbo-sacral and sciatic pain and one with secondary hypertrophic arthritis of the hips associated with "Otto pelvis" experienced jaundice and symptomatic remissions, both jaundice and remissions lasting an average of five weeks. The degree of symptomatic relief was complete for 100 per cent. of the fibrositic and for 63 per cent. of the arthritic patients; 37 per cent. of the arthritic patients had marked but incomplete relief. "Relief" implies notable or complete amelioration of the symptoms of active disease. Articular pain, active articular swelling, and muscular stiffness, soreness, and fatigue were considerably reduced or disappeared. Residual articular thickening and stiffness from deformity were, of course, unaffected. Nevertheless a moderately severe spontaneous jaundice was able to evoke a remission even in a case of long-standing very severe rheumatoid arthritis.

Four patients experienced more than one attack of jaundice; attacks of mild jaundice did not produce remissions in rheumatic symptoms, but when the jaundice was more intense the phenomenon of relief was repeated

* Communicated to the International Conference on Rheumatic Diseases, Bath, 1938.

with each attack of jaundice. No cumulative effect was noted, subsequent remissions not necessarily being longer than the first. When the phenomenon is evoked the beneficial effects of jaundice generally make their appearance promptly "with the onset of jaundice," usually within the first two or three days of the onset of visible icterus. The phenomenon was quite obvious to those affected, and they usually volunteered certain characteristic and significant remarks to relatives and friends, such as: "When the jaundice came in at the front door the rheumatism went out by the back door." Spontaneous jaundice induced a remission, not a cure. Remissions lasted from three weeks to several months; they averaged (roughly) from two to three times the average duration of the jaundice. Subsequently rheumatic symptoms returned "as before" in 48 per cent. of cases, less intensely in 39 per cent. In a few cases symptoms are still absent.

The phenomenon is apparently dependent more on the quantity than on the "type" of the jaundice: it accompanied catarrhal, infectious, or spontaneous (intrahepatic) jaundice, cinchophen jaundice, and also obstructive jaundice from stones or malignancy. A mild jaundice is apparently ineffective, the "zone of therapeutic effectiveness" seeming to begin at, and to continue above, a level of about 8 mg. of bilirubin per 100 c.cm. of serum. Four patients with mild jaundice (with a serum bilirubin below 4 or 5 mg. per 100 c.cm.) noted no relief from their rheumatoid arthritis.

Since intercurrent jaundice of several types and degrees of severity did not alleviate painful symptoms of a few patients with other conditions, such as gouty arthritis, toxic or infectious arthralgia, juxta-articular malignancy, ischaemic neuritis, post-herpetic neuralgia (Hench, 1937, 1938a, 1938b), the phenomenon appears (so far) to be relatively specific for rheumatoid arthritis and primary fibrositis. Conclusions on the specificity of the phenomenon are not final: it may be found that the phenomenon may have a wider field of exhibition (and utilization) than in these rheumatic diseases, and some more basic immunological response may be involved.

Therapeutic Implications

The therapeutic implications are obvious. An intensive study of the phenomenon—Nature's "trick way" of stopping the disease rapidly even if temporarily—may give us a clue to the pathogenesis of the disease and a clearer understanding of the immunity mechanism involved. Perhaps it may even lead to some superior method of treatment by which we can reproduce the phenomenon of remission at will. Jaundice obviously provides not a cure but a temporary control, at least of symptoms. But is it not likely that the differences between a preliminary temporary remission and the final permanent remission which we call a "cure" are merely quantitative—differences of degree and of persistence? Recently new successes in the treatment of certain diseases have rewarded those willing to follow Nature's lead, no matter how "irrational" that lead seemed, instead of continuing methods that were "rational" but relatively unsuccessful. There was no rationale for the use of malaria in neurosyphilis. Originally, behind this venture was simply the unexplained fact that "it worked." So there is to date no particular rationale for the use of "artificial jaundice" in rheumatic diseases. The history of the therapeutics of rheumatoid arthritis is filled with the ghosts of "rational treatments" which should have helped but didn't. In this instance, guided by the exposition of this phenomenon—one of Nature's revealing "slips"—a return to the empiric

might be fruitful. With this in mind we began a search for the agent responsible for the phenomenon and the mechanism whereby it is motivated.

Speculations Concerning the Factor Responsible for the Phenomenon

The responsible factor may be a chemical agent. This agent—substance X—may be a normal constituent of bile (bilirubin, bile salts, mucin, or a lipid); an abnormal hepatic substance, such as a hepatic autolysate, a product of hepatic damage; or it may be an extrahepatic substance, formed or activated elsewhere than in the liver as the indirect result of jaundice. On the other hand, it has been suggested that the responsible factor is not a chemical substance but some circumstance incident to jaundice: simple sedation, rest and reduction of trauma, dietary restriction, dehydration, counter-irritation.

1. *Bilirubin*.—The phenomenon occurs consistently in the presence of a fairly intense hyperbilirubinaemia but is generally absent when hyperbilirubinaemia is absent or slight. Thus bilirubin might seem to some to be the most likely agent. It has been suggested that perhaps the tissues of arthritic patients lack sufficient bilirubin, and jaundice supplies the deficiency. Recently Race (1937) noted that in patients with rheumatoid arthritis the icterus index and concentration of serum bilirubin were somewhat low. The bilirubin deficiency, however, was small and was not the chief cause of the low icterus index. For various reasons I believe that bilirubin may not be the responsible agent, at least not the sole or ultimate agent, though it may be an intermediary. Bilirubin is generally regarded as a substance which, physiologically, is relatively inert. Perhaps bilirubin plays no part in the phenomenon and is only an index of severity of the hepatic damage, some by-product of which is the factor responsible for the relief. Rather complete remissions of symptoms of rheumatoid arthritis may be induced by states other than jaundice, notably by pregnancy (Hench, 1938c), in which hyperbilirubinaemia does not occur though tests of bilirubin excretion may show some retention (Soffer, 1933). Nature probably does not "cure" arthritis, even temporarily, in two totally different ways. Although the mechanism for developing the agent may be different, is it not probable that in the last analysis the ameliorating agent is the same both in pregnancy and in jaundice? If this is true, one must conclude either that bilirubin is not responsible at all or that an amount of bilirubin that will produce icterus is unnecessary for the phenomenon. Perhaps in the presence of pregnancy or of jaundice a special potent form, a derivative or compound of bilirubin and not "ordinary bilirubin," is the responsible agent and one effective even in amounts that do not cause pigmentation.

Another reason for debating the possibility of bilirubin being the responsible factor is that in jaundiced arthritic patients the relation between the depth of jaundice and the phenomenon of symptomatic relief, although close, was not absolute. Frequently analgesia lasted long after the bilirubin in the serum (and presumably in the tissues) had returned to normal. Furthermore, several patients apparently noted relief even before their jaundice was visible. If that be true, either no excess of bilirubin is necessary or only a slight excess is required to produce the phenomenon. But since other observations on the ineffectiveness of slight, even if definitely visible, jaundice (4 to 6 mg. of serum bilirubin) have made the latter deduction at present untenable, no final conclusion as to the role of bilirubin can now be made.

2. *Bile Salts*.—Bile salts are apparently increased in the blood in certain types of hepatic disease with jaundice, decreased in others. Bile salts in high concentration may retard the growth of certain bacteria. Until accurate methods are available for determining their concentration in blood, the role of bile salts in the phenomenon under discussion is speculative.

3. *Hepatic Autolysate*.—It would seem more likely that the responsible agent is a product which is normal, not abnormal,

to tissues helped thereby. Nevertheless, a product of hepatic injury may be the responsible agent. The possible value of extracts of normal and abnormal livers is being investigated.

4. *Special Diet*.—In one of Pemberton's patients (Pemberton, 1920; Case 53) the joints "entirely cleared up" during acute catarrhal jaundice. He ascribed the relief not to jaundice but to "the incidental period of low feeding or even 'starvation' entailed" (Pemberton, 1920, 1935). In my cases, however, a diet low in calories or carbohydrates was not the responsible factor, since to most of the patients a "supportive diet for hepatic disease" (400 to 500 grammes of carbohydrates daily) was prescribed which they continued for from three to five weeks while in the hospital (generally with an additional 100 grammes of glucose intravenously daily) and for from three to six months thereafter. Despite this the phenomenon was not interrupted.

5. *Simple Sedation*.—It has been suggested that in jaundice the sensorium is dulled by "toxins" producing a simple sedation or non-specific reduction of pain perception. This explanation is unsatisfactory. It could hardly explain diminution of swelling and stiffness also. Furthermore, most of the affected patients were quite alert mentally and physically despite their jaundice (as my photographs and motion pictures demonstrate). If jaundice provided simple sedation, should not the patients with gout, juxta-articular malignancy, neuritis, or neuralgia have noted relief during jaundice?

6. *Counter-irritation*.—It has been suggested that jaundice provided counter-irritation, that the patients were too sick from jaundice to notice their joints. On the contrary, they particularly noticed their joints because of the surprising relief obtained therein.

7. *Rest and Reduction of Trauma*.—These were not the responsible factors. Most of the patients, freed from rheumatic pains during jaundice, were not less active but more active than for months or years, as their cited quotations indicate.

8. *Dehydration*.—This is said to relieve arthritic patients somewhat (Scully and Pemberton, 1935). In my cases dehydration was not noticeable. Indeed, large amounts of fluid were generally given, not because of dehydration, but to combat toxicity. Despite the large intake of fluid, analgesia persisted.

Speculations Concerning the Mechanism Whereby the Agent May Act

Assuming the responsible agent to be a chemical substance or compound, and not an incidental circumstance, the phenomenon may result from: (1) the correction of some chemical deficiency, (2) the correction of some chemical over-sufficiency, or (3) an immunological process involving bacteriolysis, bacteriostasis, or detoxication.

1. Though an attractive idea, it remains to be proved that jaundice provides to tissues involved in arthritis and fibrositis some chemical constituent adequate amounts of which the rheumatic patient did not previously possess.

2. Presenting the opposite view, perhaps hepatitis and jaundice correct some hyperfunctioning and not a hypo-functioning state, the hepatic damage temporarily lowering the production of some substance of which rheumatic patients have an oversupply. Were this so, severe hepatitis alone, without jaundice, might be expected to invoke the phenomenon, but it did not in one case (Hench, 1934; Case 17, first series).

3. Perhaps the agent, substance X, possesses the property of detoxication, bacteriolysis, or bacteriostasis in respect to the organisms responsible for chronic rheumatism. Bile is bacteriolytic to pneumococci. Our preliminary studies have failed to show any bacteriolytic or bacteriostatic effect on certain arthrotropic, neurotropic, or neuromyotropic streptococci *in vitro*, using concentrations of bilirubin and bile salts (alone or together) equal to or greater than those of clinical (or experimental) jaundice. Further-

more, arthrotropic streptococci could still be isolated from foci of patients enjoying the phenomenon.

I have not discussed the effect of jaundice on the physical properties of blood—colloidal osmotic pressure, surface tension, viscosity, haemoglobin-oxygen stability, and so forth. Further speculations on those phases of the problem are useless at present.

Attempts to Reproduce the Phenomenon

It was decided to administer to rheumatic volunteers the different available constituents of bile, first alone and then in combination; and first by the simpler routes (oral, rectal) and later intravenously or otherwise. Bilirubin was not used first because of reasons just noted, and because of its cost (\$25 a gramme) and relative unavailability at the onset of this work.

Bile Salts.—Many preparations are available. "Glycotauro" (Hynson, Wescott and Dunning) was given orally in doses up to 15 grammes in fourteen days. Ox gall was administered in doses up to 60 grammes in thirteen days. These doses are equal to or above those usually prescribed. The results were questionable.

Synthetic Bile Salts.—Sodium dehydrocholate ("decholin," Riedel-de Kaen) was given intravenously, orally, and in combination. Several patients received 2 grammes intravenously for from eight to twenty-one days, or the tablets (each 0.25 gramme) orally in doses up to a total of 44.5 grammes in twenty-one days. The results were questionable: some patients felt somewhat relieved, but it was evident that ordinary doses of this and the previous preparations, given alone, would not precipitate the complete phenomenon. Recently Sidel, Thompson, Rawls, and Margolis (in a discussion of my article) reached the same conclusion.

Diluted Ox Bile.—Sterile ox bile diluted in water and olive oil was given by proctoclysis, but proved irritating and was promptly evacuated.

Human Bile.—Amounts of human bile up to 2,600 c.cm. on one day (7,650 c.cm. in ten days) were given by stomach tube. Anticipating that this bile probably would circulate only through the entero-hepatic circulation and never reach the general or articular circulation, I was not surprised that the concentration of serum bilirubin was not increased and that no relief resulted. Patients took the bile well; one took it with pleasure, saying it increased his appetite.

Liver Extracts.—Ordinary doses of commercial liver extract which I have occasionally used in treating arthritic patients with secondary or with coincident pernicious anaemia never appeared to affect articular symptoms. This has also been the observation of Drs. George Minot and William Murphy (personal communication). Hence this method of approach has not been extensively explored. Reasoning that the effective agent might be a product of hepatic degeneration, Margolis (1937) gave McElroy's liver autolysate intravenously to two patients with rheumatoid arthritis. Exacerbations of pain, stiffness, and soreness were obtained.

Transfusions of Highly Jaundiced Blood.—To my knowledge, jaundiced blood has not heretofore been deliberately used for transfusion. Hoping that potent amounts of substance X might be present in portions of jaundiced blood available for transfusions, four arthritic patients received one to four such transfusions. "Round-robin transfusions" were arranged: non-arthritic jaundiced patients with various hepatic disorders donated amounts of (Wassermann-negative, sterile) "bad blood" in return for twice as much "good blood" from healthy donors; the jaundiced blood was injected into non-jaundiced arthritic patients in the usual manner, with only a slight reaction or no more than from any transfusion. One patient in her fourth transfusion received 800 c.cm. of jaundiced blood containing 21 mg. of bilirubin per 100 c.cm. (actually only 168 mg. of bilirubin). The next day she insisted that she had less pain; if so, relief was transient, and the serum bilirubin was immaterially increased.

Artificial Jaundice.—Since these various methods used to reproduce the phenomenon were employed only on small numbers of patients, they should not be hastily dismissed as useless. But obviously the complete phenomenon provided by spontaneous jaundice was not being reproduced thereby. Rather than persist in these methods it was decided to postpone further investigation along these lines and to attempt to obtain by some other method an effect comparable to the phenomenon described, not the slow equivocal type of improvement which the current methods already provided. It seemed necessary to effect a reproducible, relatively harmless type of jaundice in order to study satisfactorily the physico-chemical intricacies of the phenomenon.

Toluylenediamine Jaundice.—Certain studies (Wolff, 1934; McGowan, 1935; McGowan, Bollman, and Mann, 1936) suggested that toluylenediamine might be a suitable substance to use in the first deliberate attempt to induce jaundice experimentally in man. Toluylenediamine jaundice in animals was intense, was rather controllable, was intrahepatic in type, and produced no significant detectable functional or pathologic residue. In June, 1936, an arthritic patient who was discouraged after thirteen years of suffering from a condition that had progressed in spite of all manner of therapy elected to take toluylenediamine orally. Contrary to expectations the induced jaundice was wholly of the haemolytic type; it was transient and rather mild, the maximal concentration of bilirubin being only 6.3 mg. (direct reaction), not entering the zone of therapeutic effectiveness. No relief of joint symptoms resulted. The chemical produced considerable gastro-intestinal irritation. Further details will be reported elsewhere.

Induced Hyperbilirubinaemia.—More recently, Thompson and Wyatt (1937, 1938) noted that the intravenous administration of bile salts alone (decholin, 2 grammes daily for nine to twelve days) was without beneficial effect in ten cases of rheumatoid arthritis, as were injections of bilirubin alone (10 to 15 mg. per kilogramme daily for several days) in three cases. They noted, however, that injections of bilirubin (10 mg. per kilogramme) and decholin (40 mg. per kilogramme) in combination produced an ameliorating effect, "which apparently duplicates the effects" of clinical jaundice. The bilirubin-decholin combination produced a slightly higher and more persistent hyperbilirubinaemia than injections of bilirubin alone. Except for a few febrile reactions no evidences of toxicity were noted in the patients or animals that had been given the injections.

At the last conference of the American Rheumatism Association (June, 1937) Thompson presented the preliminary results of these experiments. Injections of bilirubin and decholin were given to ten patients daily for from seven to eleven days. Each day the injected bilirubin was rapidly but incompletely excreted, so that with repeated doses the tissues retained enough to produce definite hyperbilirubinaemia and icterus. Thompson and Wyatt reported that in these ten cases diminished swelling was noted after from one to nine injections. Analgesia (at first partial) was observed after from one to seven injections and persisted for varying periods, the shortest period being twelve days. At the time of their report analgesia had been maintained in one case for five months, in another for five and a half months, in others for two months, one month, and one month respectively. In November, 1937, I visited Drs. Thompson and Wyatt. Their results at that time (which are here given with their permission) were as follows. They had administered from six to twelve injections of bilirubin and decholin to a total of thirteen patients whose disease had lasted from three to eight years. Of these thirteen cases, "long remissions" (from two to eight months) had been precipitated in four cases, "short remissions" (five to forty days) in six, and no results had been obtained in three. (Two other patients were under treatment.) With regard to the three cases in which no results were obtained: (1) one patient with muscular pains stopped treatment after six doses; (2) a woman with severe rheumatoid arthritis was unrelieved after twelve doses; and (3) a spondylitic patient noted slight analgesia after the second dose, and considerable analgesia but no increased mobility after nine doses; the analgesia persisted only ten days, after which he had a severe exacerbation.

Preliminary Results with Induced Hyperbilirubinaemia

A few weeks before presenting his preliminary results Dr. Thompson kindly acquainted me with this work in order that I might attempt its confirmation. The technique of preparation and administration is not as simple as it sounds. It is not simply a question of dissolving bilirubin in any alkali, adding bile salts, and then injecting the mixture. To date it appears that the solution must be made fresh daily (a matter of about two hours' work), administered promptly, and, according to Thompson, kept from sunlight constantly (possibly to prevent oxidation of bilirubin; at least it tends to minimize reactions). It remains to be proved how necessary some of these procedures are. Most commercial bilirubin is rather impure. Although the samples of bilirubin we are both using are becoming purer, they still contain impurities. The strongly alkaline mixture continues to irritate the veins and causes frequent thromboses, so that the matter of giving a number of consecutive daily injections often becomes a problem. In an attempt to avoid thrombosis we buffered the solution to approximate neutrality just before the injection in two cases. This markedly altered the results; no significant hyperbilirubinaemia and no symptomatic relief was obtained. In spite of technical difficulties, however, we at the clinic have at least partially confirmed the work of Thompson and Wyatt. By this procedure one can produce a definite, apparently non-toxic pigmenting hyperbilirubinaemia. Using the larger dose of bilirubin (15 mg. per kilogramme) more frequently than Thompson, we have produced degrees of hyperbilirubinaemia in which the peak concentrations (just after the solution is injected) have reached 20 to 35 mg. and the retention levels twenty-four hours after injection (and just before another injection) rose to as high as 12.5 mg. of bilirubin per 100 c.cm. of serum.

To date my colleagues and I have treated twelve patients—eleven with rheumatoid arthritis and one with primary fibrositis. Rarely obtaining any significant effect from six to twelve injections, we have sometimes given twelve to twenty and in a few cases from twenty-five to thirty consecutive daily injections. Little or no benefit was obtained in five cases (including the two in which the solutions were buffered). One patient had a rather complete temporary remission in symptoms, but only for about three weeks, which is the longest and most definite effect obtained. Short incomplete remissions apparently resulted in six cases for a few days only: in three of these six cases the reduction in symptoms seemed slight but definite; in the other three it was more definite but was still incomplete and very transient. One of these six patients accepted two courses of injections: the first course included seventeen doses, the second twelve doses.¹ He was markedly icteric, but the effect was mild, if there was any. At the start, attempting by correspondence to collaborate in the development of a new technique, we made three slight changes in technique which we believed were insignificant.² Correcting these "differences," however, has not brought about a relief com-

¹ The first seventeen doses were prepared by our "modification" of Thompson's technique, but the twelve doses of the second course were prepared exactly according to Thompson's technique.

² In the method of Thompson and Wyatt bilirubin is dissolved in monohydrated sodium carbonate; we used anhydrous sodium carbonate, solutions in both cases being one-tenth normal. When the bilirubin was thoroughly dissolved Thompson filtered the solution through a Seitz filter. To facilitate the Seitz filtration we first filtered the solution through a thin layer of infusorial earth. Decholin was added by Thompson after the Seitz filtration, by us before the filtration. These "differences" in technique seem immaterial.

parable to that produced by spontaneous jaundice. The failure to produce constantly any lasting relief by such injections has convinced me that it is necessary to study this problem from many other angles in order to establish the influence of the various factors involved.

Preliminary Appraisal.—It is too early to evaluate the procedure fully. By it one can produce an apparently harmless artificial "jaundice" or hyperbilirubinaemia which may be utilized to advantage in the study of a number of physiological and clinical problems. Only by some such method can we determine what part, if any, bilirubin plays in the phenomenon which spontaneous jaundice induces. Regardless of the slight, and to my way of thinking unimportant, differences in technique, my results, and those of Thompson and Wyatt, speak for themselves. A number of my patients have been made markedly icteric and had concentrations of serum bilirubin that should have been effective were bilirubin in just any form the potent factor; the results, however, have been equivocal or incomplete. Obviously the method is not yet reproducing the full effect which spontaneous jaundice evokes. But the fact that any effect, no matter how incomplete or transient, can be so induced, even inconstantly, seems significant. So far, however, one must clearly differentiate the effects of spontaneous jaundice from those of induced hyperbilirubinaemia.

Since the results were so often equivocal, the procedure of inducing hyperbilirubinaemia has been difficult to evaluate. It seems to me best to regard it as a worthy preliminary venture which may provide a rather crude and inconsistent approximation of the more dramatic and complete effect of spontaneous jaundice. Certainly in its present form it is by no means a "control of arthritis"; nor is it yet a practical procedure, because it is expensive, time-consuming, and (most important) inconstantly and incompletely effective. Regarding it as promising research, I agree with Thompson that to exploit the use of bilirubin and bile salts for the treatment of arthritis at this time is unwarranted and most undesirable.

Summary and Conclusions

Jaundice involves a physiological reaction which is antagonistic to the continuation of active symptoms of rheumatoid arthritis and primary fibrositis. With the onset of any one of several types of jaundice, rather dramatic remissions in rheumatic symptoms, lasting from three to 104 weeks, occurred in nineteen cases of rheumatoid arthritis, in nine of primary intramuscular or peri-articular fibrositis, in two of lumbo-sacral and sciatic pain, and in one of secondary hypertrophic arthritis of the hips. Remissions averaged (roughly) from two to three times the average duration of the jaundice and affected symptoms of active disease; residual articular thickening and disability from deformity were unaffected.

The phenomenon depends more on the quantity than on the quality (or type) of jaundice, a certain intensity of jaundice being required. Since intercurrent jaundice of several types and various degrees of severity did not alleviate symptoms of certain other painful articular and neuritic diseases, the phenomenon may be relatively specific for rheumatoid arthritis and fibrositis. This conclusion is tentative; perhaps the exhibition and application of the phenomenon may be possible in other conditions.

The therapeutic implications are obvious: a study of the phenomenon may enhance our knowledge of the pathogenesis of these diseases and may lead to some superior method of treatment. The responsible agent and

the mechanism whereby it operates have not been identified; certain hypotheses concerning them have been entertained. Several methods involving the administration of various components of bile and the production of artificial jaundice and induced hyperbilirubinaemia are being used in an attempt to reproduce the phenomenon. "Therapeutic jaundice" is an attractive term, but even if what it implies can be successfully accomplished, it should be regarded not as an end in itself but as a means to an end, a rather crude form of treatment which is just a step, but perhaps an important one, on the way to the refined therapy of the future.

Regardless of what further investigations bring forth, four conclusions are made now:

1. The condition of jaundice is not entirely malevolent; it may initiate a phenomenon distinctly, if temporarily, beneficial to patients with certain diseases, particularly rheumatoid arthritis and fibrositis.

2. Rheumatoid arthritis and fibrositis can no longer be regarded as necessarily relentless uncontrollable diseases for which no really satisfactory rapid method of control should ever be expected. Certain of their pathological changes may be permanent, but their pathological physiology is more rapidly reversible than previously supposed; indeed, it may be dramatically reversible.

3. Regardless of the supposed validity of the infectious theory, obviously rheumatoid arthritis and fibrositis can be profoundly influenced by a phenomenon primarily chemical.

4. Nature possesses a highly effective method of producing dramatic remissions involving a phenomenon which is precipitated more rapidly by jaundice than by any other physiological or therapeutic method. The next step belongs to the future. It is important for us to identify Nature's dramatic, if accidental, antidote.

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