

REDUCTION OF BLOOD PRESSURE ASSOCIATED WITH THE PYROGENIC REACTION IN HYPERTENSIVE SUBJECTS¹

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The use of inulin for the measurement of glomerular filtration in man was introduced in 1934 (1). It was subsequently observed that some samples of inulin may be heavily contaminated with a pyrogenic substance (2, 3), probably of bacterial origin, which induces, in addition to the commonly observed chill and fever, a marked renal hyperemia (4, 5, 6) and, particularly in hypertensive subjects, a fall in blood pressure. A suitable course of amidopyrine, administered prior to the injection of pyrogenic inulin, prevents the occurrence of the chill and fever without preventing the renal hyperemia (5, 7) and fall in blood pressure. It has been our experience that renal hyperemia and reduction of blood pressure also follow the intravenous administration of other pyrogenic substances, such as glucose, distilled water (with salt), and commercial saline, as well as triple typhoid vaccine, and it seems probable that the physiological response is generic.

In the theory that renal ischemia is the primary causal factor in the genesis of hypertension, it would be supposed that the repeated induction of renal hyperemia might have a favorable effect upon the hypertensive process. With the intent of examining this point, we repeatedly administered pyrogenic inulin to several hypertensive patients for a period of some days or weeks; a sustained reduction in blood pressure was in fact obtained, but the type of blood pressure response, coupled with other information reported below, has led us to conclude that the hypotensive action of pyrogenic inulin, as of the other pyrogens discussed in this paper, does not represent a fundamental correction of the hypertensive process but rather a complex response on the part of the circulatory system. Since pyrogens are a frequent contaminant of materials of organic origin intended for parenteral administration, we feel that the observations reported below may have some

practical value, in addition to their inherent physiological interest.

Some of the observations recorded here are drawn from our general experience, but the paper is primarily concerned with special observations made on nine subjects, eight with essential hypertension and one with chronic diffuse glomerulonephritis. These subjects were selected from the Nephritis and Hypertension Clinic of the New York University College Clinic and the Third (New York University) Medical Division of Bellevue Hospital. While in the hospital they were confined to bed rest for a period of ten to twenty days, until the blood pressure, which was determined by the auscultatory method at frequent intervals throughout the day, had become stabilized. Three subjects (M. G., F. T., R. L. in 1939) received pyrogenic inulin intravenously, and four subjects (F. K., 1939, P. K., M. T. and S. D., 1941) received triple typhoid vaccine intravenously. While this study was in progress, the effect of subcutaneous injections of tyrosinase (8, 9, 10) on renal blood flow and blood pressure was being studied in three hypertensive subjects (A. B., M. T. and F. T.), and since all three exhibited a febrile reaction during treatment, they are included in this report. We are also including observations on the blood pressure in one subject (K. S.) who developed a febrile reaction following cystoscopic examination.

PYROGENIC INULIN

What we consider to be a fairly typical picture of the immediate blood pressure response to a single dose of pyrogen (Pfanstiehl inulin, lot no. 268) in a hypertensive subject is illustrated by R. L., as shown in Figure 1. This patient was one who received repeated treatment with pyrogenic inulin, but only the first two occasions are illustrated. On the first occasion, as shown in Figure 1, the renal blood flow was followed by

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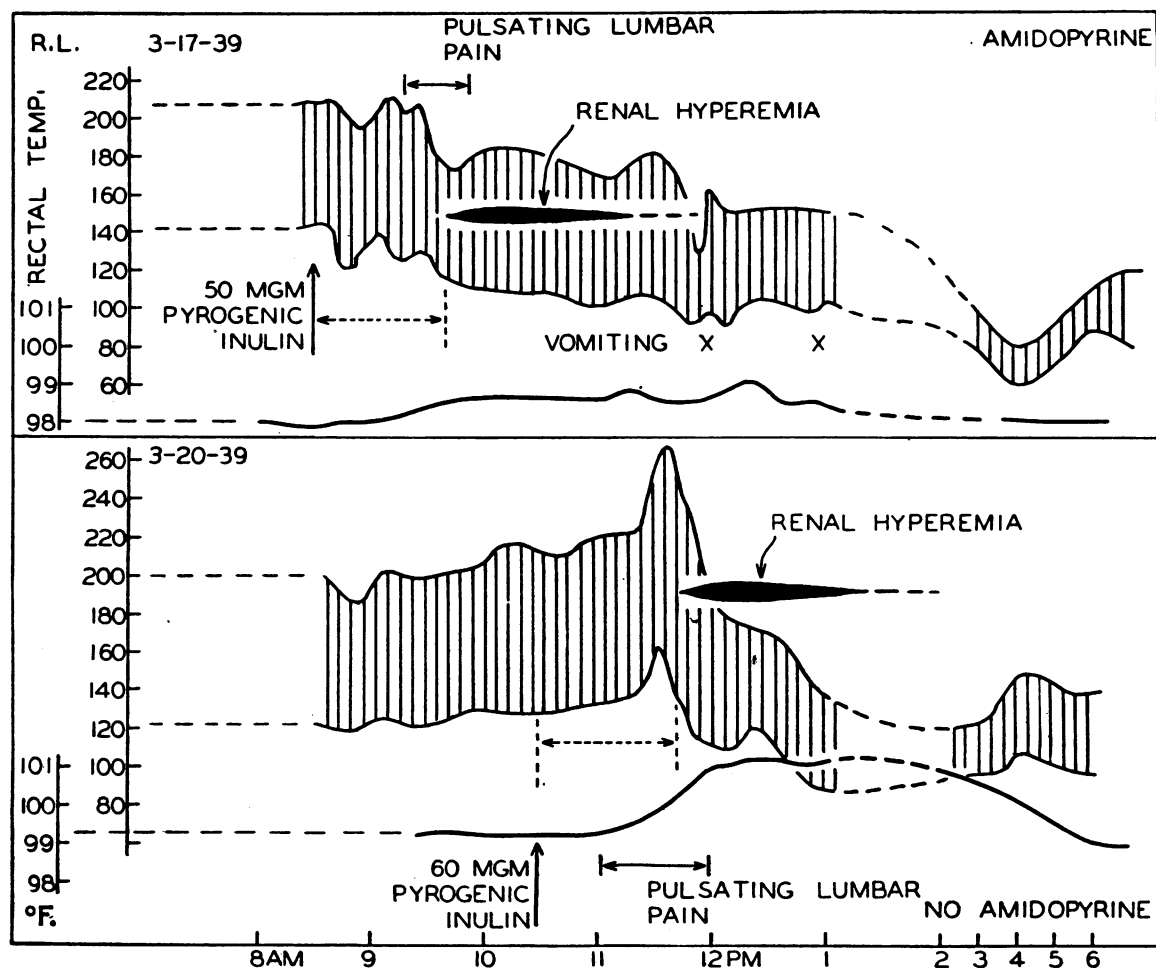


FIG. 1. HYPOTENSIVE EFFECT OF PYROGENIC INULIN ADMINISTERED INTRAVENOUSLY TO A HYPERTENSIVE SUBJECT, WITH AND WITHOUT PREMEDICATION WITH AMIDOPYRINE

The renal plasma flow was followed on the first occasion only, but it is fairly reproducible in respect to time and consequently has been interpolated in the lower graph. Note the very low pressure period which follows long after renal hyperemia is over. This subject never developed a marked fever under continued treatment.

means of the clearance method; as reported elsewhere (4, 5), a latent period of sixty to ninety minutes supervenes before the development of renal hyperemia. Renal clearances were not followed on the second occasion, but we have indicated the probable time of appearance and duration, as judged from our experience with other patients.

The blood pressure response in patients not premedicated with amidopyrine usually shows three more or less distinct phases: (a) a fleeting pressor phase, which appears from sixty to ninety minutes after pyrogen injection (see Figure 1 bottom, and also Figure 6 of Chasis *et al.* (4)

and Figure 4 of Smith (5)); (b) a phase characterized by a moderate fall in diastolic and systolic pressures, but with a well maintained pulse pressure, which immediately follows (a) and coincides roughly with renal hyperemia; and (c) a low pressure phase characterized by marked reduction in both systolic and diastolic pressures and a shallow pulse pressure, which appears four to six hours after the injection of pyrogen and which may last for several hours. The degree of blood pressure reduction in this delayed phase is highly variable, the phenomenon being slight or absent in normal subjects.

As shown in Figure 1, premedication with

amidopyrine (0.6 grams every four hours for five doses) blocks the pressor phase (*a*) and the rise in body temperature, but it does not block the renal hyperemia and the simultaneous changes in blood pressure described under (*b*), nor the delayed extreme reduction in blood pressure (*c*). With or without amidopyrine, the delayed reduction in blood pressure (*c*) may be so prolonged that the pressure is still at reduced levels the next morning.

By the repeated administration of moderate amounts of pyrogen daily, the blood pressure in hypertensive subjects can be maintained at reduced levels. Figure 2*A* (M. G.) shows the effects of daily administration of pyrogenic inulin. This patient received treatment during two periods of twelve and eleven days respectively, each injection (50 mgm. to 300 mgm. inulin lot no. 268) being followed by a febrile reaction. During the administration of pyrogen, the daily average blood pressure (six or more readings exclusive of the pressor phase) remained at significantly lower levels than during the control period, and the hypotensive effect persisted for the twelve days of observation following the last injection. To what extent the maintained reduction in blood pressure is attributable to the persistence of the more acute hypotensive action described under (*c*), or to other and unknown factors, cannot be said.

In two other patients, a similar sustained reduction in blood pressure was produced by the repeated intravenous administration of pyrogenic inulin. In none of these was there evidence of immediate or delayed (two years) injurious effect, as discoverable by repeated urinalyses and renal clearance tests.

TRIPLE TYPHOID VACCINE

Figure 2*B* (F. K.) shows the effect on the blood pressure of repeated administration of triple typhoid vaccine intravenously. Sixteen injections (0.05 to 5.5 cc. of New York City Department of Health standard vaccine) were given over a period of thirty-eight days, each injection being followed by a febrile reaction. The blood pressure fell markedly following the first injection and was maintained at a low level throughout the period of treatment.

Two other hypertensive subjects were given

triple typhoid vaccine intravenously. P. K. was treated daily for eleven days with a sustained hypotensive effect. The results are similar to those obtained on F. K. and need not be illustrated.

Patient S. D. merits detailed discussion. She was a sixty-year-old white female whose hypertension had been discovered at the age of fifty-two. There was no history of diminution in cardiac reserve and no clinical evidence of congestive heart failure. Examination of the ocular fundi showed in moderate degree the vascular changes associated with hypertension. The blood pressure ranged from 244/136 to 164/110 mm. Hg during a ten-day control period on bed rest. Proteinuria and hematuria were absent; the specific gravity of the urine ranged from 1025 to 1005; the urea clearance was within the normal range and the blood non-protein nitrogen was 35 mgm. per cent. The administration of amidopyrine (0.6 grams every four hours for five doses) on the first day of premedication produced nausea and vomiting; triple typhoid vaccine (0.02 cc.) was nevertheless given intravenously on the second day and induced a reaction consisting of severe bilateral lumbar pain and pain in left anterior chest. The rectal temperature remained at 98.8° F. and the blood pressure level did not change. Amidopyrine was continued during the third day, but no vaccine was given. Amidopyrine was continued for the fourth day and triple typhoid vaccine again was withheld; the nausea and vomiting had now subsided and the patient was comfortable. On the fifth day, still continuing amidopyrine, the intravenous administration of vaccine (0.05 cc.) was followed in one hour by violent throbbing lumbar pain and vomiting, and three hours after the injection the patient went into peripheral circulatory failure and became unconscious. The blood pressure fell to 80/52 mm. Hg, the heart rate remaining at 78 to 86 throughout the reaction. The patient recovered consciousness in half an hour, the blood pressure rising to 130/76, only to fall again in seven hours from the injection to 70/50, with relapse into unconsciousness, accompanied by pallor and sweating. Consciousness was shortly recovered and in an hour the circulatory status had improved. The patient fully recovered from the episode, and in

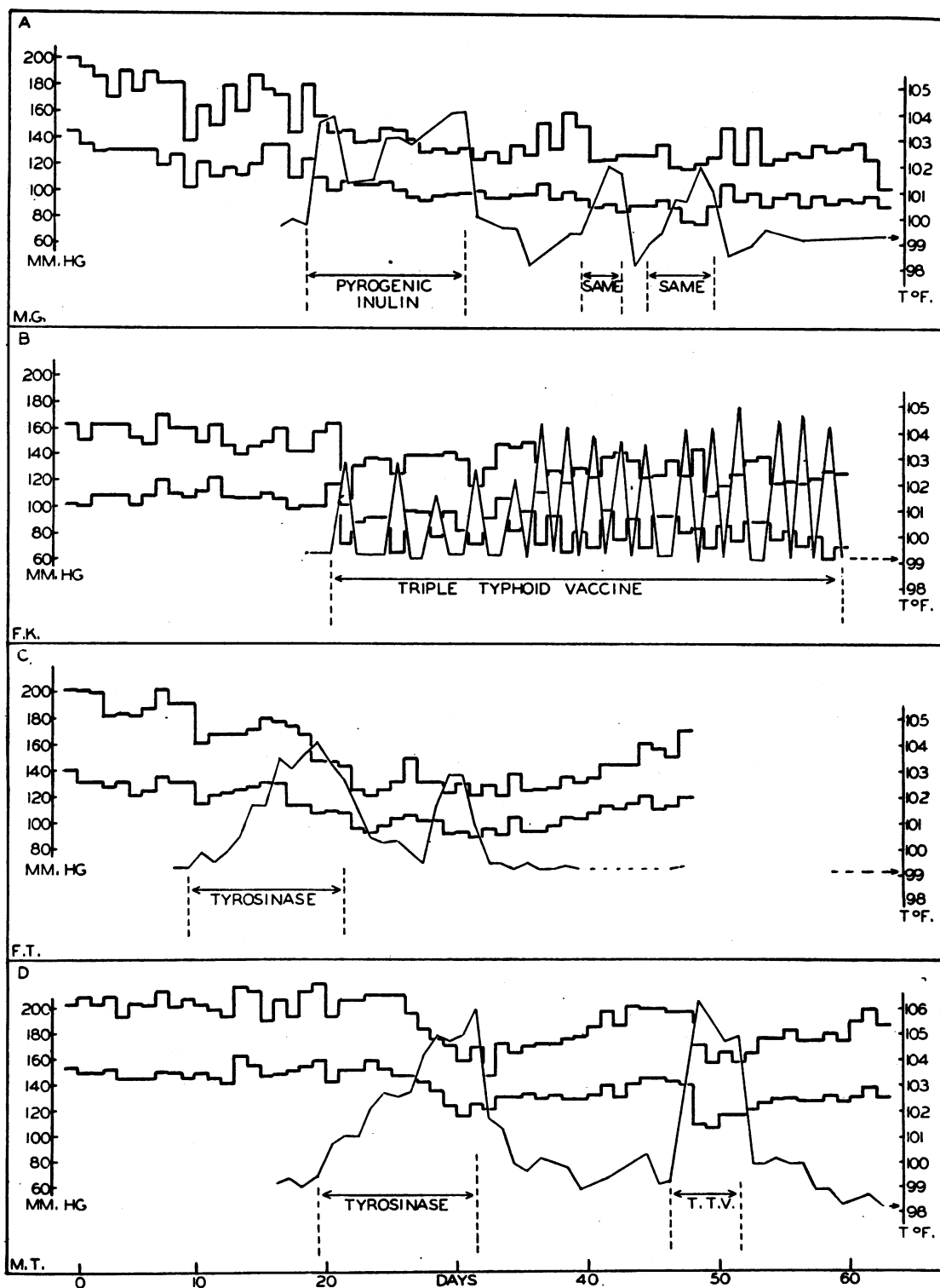


FIG. 2. BLOOD PRESSURE AND RECTAL TEMPERATURE IN SUBJECTS RECEIVING PYROGENIC AGENTS

A. Prolonged hypotensive effect of repeated intravenous injections of pyrogenic inulin in a subject with essential hypertension.

three days the blood pressure had returned to the control level.

Since amidopyrine was continued throughout treatment without ill-effects certainly attributable to this drug, and with recovery from nausea, and since the episode of circulatory failure followed the administration of triple typhoid vaccine, we believe that this patient illustrates an instance where the hypotensive action of pyrogenic material itself resulted in dangerous embarrassment of the circulatory system. It may be specially noted that there was no fever at any time during the five days of treatment.

TYROSINASE

Tyrosinase was administered subcutaneously in the thigh to two subjects with essential hypertension (A. B., not illustrated, and M. T.), and to one subject (F. T.) in the hypertensive stage of chronic diffuse glomerulonephritis. In all three there developed, at the site of injection, local reactions varying from a localized area of pigmented erythema to a widespread, edematous, tender, cellulitis-like area with inguinal adenopathy. In all three subjects during the period of treatment there occurred persistent fever, associated with malaise, prostration, anorexia, dehydration, and loss of weight.

Figure 2C records the effect of tyrosinase (1300 to 7800 catacolase units)² on the blood pressure of subject F. T. The injections were given daily for twelve days. With the development of fever, the blood pressure fell to significantly lower levels and tended to return to the control level as the local reactions at the site of injection subsided and the body temperature returned to normal. (The second rise in temperature, after the injections had been discontinued, was associated with continuing severe local reaction.)

² Two weeks after the end of this therapy, the tyrosinase preparation had lost 40 per cent of its catacolase activity. The pH (7.3) had not changed.

We are indebted to Dr. John M. Nelson of Columbia University for supplying the tyrosinase.

B. Prolonged hypotensive effect of repeated intravenous injections of triple typhoid vaccine in a subject with essential hypertension.

C. Prolonged hypotensive effect of repeated subcutaneous injections of tyrosinase in a subject in the hypertensive stage of chronic diffuse glomerulonephritis.

D. Prolonged hypotensive effect of repeated subcutaneous injections of tyrosinase, followed by a second period of treatment with triple typhoid vaccine, in a subject with essential hypertension.

Figure 2D shows the response of the subject (M. T.) with essential hypertension, who was treated on two occasions: first, with tyrosinase (see F. T. for dosage) administered subcutaneously; and after a second control period in which the blood pressure had returned to its original hypertensive level, with triple typhoid vaccine (1.0 to 3.0 cc.), administered intravenously. A hypotensive effect was produced on both occasions.

In all three patients treated with tyrosinase, the blood pressure fell only after elevation of body temperature had occurred.

POST-CYSTOSCOPIC REACTION

Figure 3 (K. S.) shows the blood pressure response in a patient with essential hypertension during a post-cystoscopic febrile reaction. Five hours following cystoscopy the patient had a severe chill lasting for one-half hour, followed by a rise in body temperature which then remained constantly elevated. The blood pressure started to fall following the first chill and remained at a reduced level throughout the febrile period. The

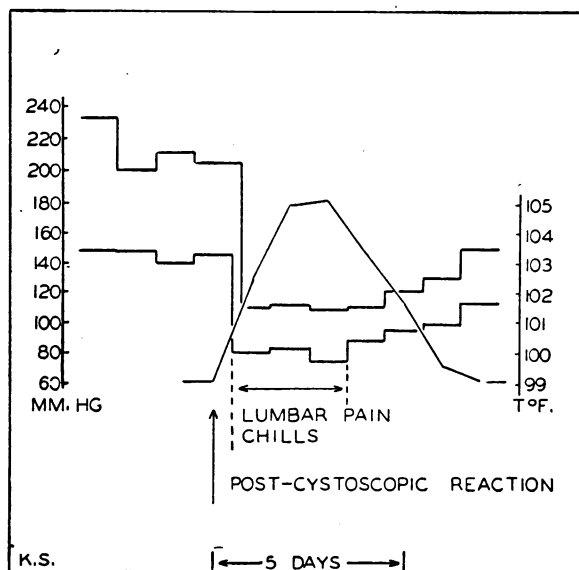


FIG. 3. MARKED FALL IN BLOOD PRESSURE ASSOCIATED WITH A POST-CYSTOSCOPIC FEBRILE REACTION IN A SUBJECT WITH ESSENTIAL HYPERTENSION

patient did not show signs of circulatory inadequacy during the hypotensive phase and had no subjective complaints after the fever had subsided.

It is not uncommon for acute infectious febrile states to be accompanied by a fall in blood pressure in hypertensive subjects, a phenomenon which is generally recognized. The subject K. S. is reported here chiefly as a striking instance of this response.

DISCUSSION

The pyrogenic reaction, although it can be induced in all subjects, varies not only in its manifestations but also in its severity in different subjects. Characteristically, it consists of a sensation of chilliness or a severe chill, pulsating lumbar pain, headache, fever, and renal hyperemia, with the sequence of complex vasomotor responses briefly described earlier in this paper. In some individuals there may also occur nausea, vomiting, substernal pain, cyanosis, and, in occasional instances, peripheral circulatory failure. Premedication with amidopyrine blocks the chill, the pressor phase in the vasomotor response, the rise in body temperature, and all subjective symptoms except occasionally the pulsating lumbar pain, without blocking the renal hyperemia or the fall in blood pressure which, as represented by the second phase, coincides with the renal hyperemia, or as represented by the third phase, consists of a more severe hypotensive action, long outlasting the renal hyperemia. During this prolonged hypotensive action, the blood pressure may fall to alarmingly low levels; this phenomenon is, however, variable in its occurrence and severity, and cannot be predicted.

Pyrogen itself is apparently not a depressor substance or vasodilator, since it has no perceptive immediate action on blood pressure, as determined by the auscultatory method, or on renal blood flow; and a latent period of about ninety minutes typically intervenes before the blood pressure begins to fall. The vasomotor responses occurring in patients receiving pyrogen are undoubtedly complex, and also probably differ in normal and in hypertensive subjects.³ The initial pressor

phase appears to be a neurogenic vasoconstriction associated with the autonomic disturbance which is elicited by pyrogenic agents in general. The second phase, wherein both systolic and diastolic pressures are moderately reduced, with typically a wide pulse pressure, perhaps reflects the decrease in peripheral resistance associated with the observed dilatation of the renal vascular bed. Dilatation in other organs cannot, of course, be excluded. The more severe reduction in blood pressure which occurs after several hours, and which, as we have said, is variable and unpredictable, and more severe in hypertensive than in normal subjects, may represent a more extreme state of vasodilatation but the reduction in pulse pressure suggests the presence of a diminished cardiac output or other adverse reactions in the circulatory system.

The pyrogenic reaction has been observed by us to follow the administration of triple typhoid vaccine, pyrogenic inulin, and tyrosinase, and it has also been observed during a post-cystoscopic febrile reaction. We have also seen the reduction in blood pressure following the intravenous administration of pyrogenic normal saline and glucose. Though different pyrogens may be involved in these reactions, it is well known that a pyrogenic substance is characteristic of Gram-negative bacteria, and it has been demonstrated that a substance can be extracted from *D. dysenteriae* and *B. coli*, which is composed of a polysaccharide, a phospholipin, and a polypeptide-like molecule (11, 12), and which is capable of producing a reaction in rabbits similar in its general effects to the one described in this study.⁴ Since many post-cystoscopic reactions are the result of a transient *B. coli* bacteremia,⁵ it may be that substances arising in Gram-negative bacteria are the common active factors in all the pyrogenic reactions discussed above.

⁴ Personal communication from Dr. Rene J. Dubos. The examination of the physiological effect of these fractions is now in progress, in collaboration with Dr. Dubos.

⁵ A bacillus of the *B. coli* group was found to be the invasive organism in 17 of 25 patients who had a bacteremia following cystoscopy, in work to be reported by Dr. Justina Hill of the James Buchanan Brady Urological Institute, Johns Hopkins Hospital. This is not meant to indicate that every post-cystoscopic febrile reaction is associated with a bacteremia.

³ These hemodynamic responses are being studied in more detail at the present time, particularly with reference to cardiac output.

Our observations on tyrosinase are included in this report because of the relationship between reduction of blood pressure and fever; in no case did we observe blood pressure to be reduced until the local reaction had gone far enough to induce some febrile response. Our results, however, do not demonstrate that tyrosinase is without specific effect on blood pressure, and the fact that heating destroys the hypotensive action of tyrosinase preparations (Schroeder, personal communication), where pyrogen is generally resistant to heating, argues in favor of a specific action.

Bacterial contamination is allegedly responsible for the pyrogenic properties of some samples of distilled water; and any material prepared chemically with ordinary water, which itself is frequently contaminated with pyrogenic organisms, must be suspected. It has been our experience that once inulin is contaminated with pyrogen, repeated purification by recrystallization from water or alcohol-water mixtures fails to remove the pyrogen, which can be removed only by effective absorbents; and if organic preparations intended for parenteral administration were once contaminated with pyrogen, either from the raw materials, the water used in manufacture, or by bacterial growth during the course of preparation, effective quantities might be carried through repeated purifications. It is also possible that the local tissue reaction which sometimes follows the injection of foreign material may give rise to an endogenous factor having a vasomotor action similar to that of bacterial pyrogen, since such local reactions are frequently accompanied by fever.

The fact that amidopyrine blocks the rise in body temperature, without blocking the hypotensive action and the renal vasodilatation induced by pyrogenic agents, may bespeak a dual nature in pyrogen itself, or merely a dissociation of the febrile and vascular responses within the body. This, like many other problems associated with the pyrogenic reaction, invites further investigation, but, until the question is answered, it seems unwarranted to accept the febrile response itself as an adequate criterion of the presence or absence of powerful, delayed-action, vasomotor agents of the type studied here.

We have observed no clinical signs of injurious action in the patients treated here, as judged by

urinalyses and renal clearance studies, but it is known that bacterial extracts administered in closely repeated doses may produce delayed necrotic lesions in the kidneys (Shwartzman phenomenon (13)), and such substances should be administered with due consideration of this fact. It should also be noted that pyrogenic material may induce an alarming circulatory crisis, as illustrated by our patient S. D., in consequence of the delayed-action vasomotor effects.

SUMMARY

Blood pressure can be reduced significantly in hypertensive subjects by the intravenous administration of pyrogenic material (pyrogenic inulin, triple typhoid vaccine, tyrosinase), and it can be maintained at reduced levels by the repeated injections of this material. This hypotensive effect can be obtained without a rise in body temperature by premedication with amidopyrine.

The mechanism responsible for the persistent blood pressure reduction is unknown, but, from the more immediate effects of pyrogen, it appears to be attributable in part to an adverse or asthenic action on the cardiovascular system, rather than a correction of the fundamental disturbance underlying the hypertensive process.

One instance of a marked reduction in blood pressure in a hypertensive subject during a post-cystoscopic febrile reaction is illustrated. Such reactions are reported to be attributable to a transient *B. coli* bacteremia, and the reduction of blood pressure here, and in other acute infections, may be associated with the pyrogenic reaction associated with the infection.

Whenever the blood pressure of a hypertensive subject is reduced by the parenteral administration of a foreign organic material, this pyrogenic type of response should be excluded before a specific hypotensive property is attributed to the agent used. And any pyrogenic material should be administered cautiously, since it may induce an alarming degree of peripheral circulatory failure, as illustrated by one of our subjects (S. D.).

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