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Staff Meeting Report

Changing Medical Practice*

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At this meeting of the staff of the University Hospitals at Homecoming time I would like, as the representative of the State Medical Association, to discuss three closely related elements of medicine, namely: who practices medicine, what influences are changing the practice of medicine, and how we, as teachers and as practitioners can maintain the high standards essential to our profession.

To start with the obvious: This is a medical school. It confers the degree of Doctor of Medicine, and its graduates go on to teaching and research, but mostly to the practice of medicine. The question promptly arises, Are your graduates and other doctors of medicine the only ones who practice medicine? Of course they are not, and in fact doctors of medicine have never been the only practitioners of medicine or of healing. Originally, healing was a function of the priests, and the sick came to the temple for help. At about the time of Hippocrates the first real physicians appeared whose primary function was healing. In the early Middle Ages medicine was often combined with alchemy. The specialties sometimes grew out of the profession of medicine but sometimes appeared from outside and after being brought up to proper standards became part of medicine itself, as in the case of the barber surgeons.

Throughout history methods of healing have been employed other than those properly recognized as "medical": One type of healing was that performed by the witch doctor, once prevalent among the Indians of North America, and still present in Africa and among the Australian aborigines. These surely partook of the fact if not the technique of faith healing. The masks, the motions, the potions, and the stagecraft of the medicine man must have been impressive, and perhaps these are carried over to the physician of the modern television play and possibly even to our own radioisotope laboratories.

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*This report was given at the Staff Meeting of the University of Minnesota Hospitals on October 17, 1958.

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Only a few hundred years ago the King's touch was regarded as the cure for scrofula, as attested to by outstanding surgeons of the day.

The "weapon ointment," or *unguentum armarium,* held to be a potent cure for injuries received in battle, was compounded in a specified way of such peculiar ingredients as "portions of a mummy, . . . human blood, and . . . moss from the skull of a thief hung in chains." In its use the wound was washed and bandaged and the ointment was carefully applied to the weapon that had inflicted the wound. Lord Bacon speaks of the weapon ointment in his *Natural History* as having in its favor the testimony of many, although he said he "as yet is not fully inclined to believe it."

"Sympathetic powder" was somewhat similar to the weapon ointment, but instead of being applied to the weapon inflicting a wound, it was applied to a part of the patient's clothing, with or without the patient's knowledge. This substance turned out to be powered blue vitriol, also prepared in a very special way.

In 1796 Dr. Elisha Perkins of Connecticut brought out Perkins Tractors: These were two pieces of metal, one iron and the other brass, which, when drawn over an area of inflammation supposedly drew out the poison and thus cured the patient. For fifteen years they not only were accepted and used by the public but also were recommended by ministers, generals, and public officials. The tractors cost about eighteen cents a pair to make and sold for about five dollars. Dr. Perkins was expelled from the Connecticut Medical Society in 1797, one year after he introduced the device, and by 1810 the tractors had disappeared from the medical scene.

Also in 1796 Samuel Hahnemann, a German physician, published his first paper on homeopathy. In 1805 he published his first work, in 1810 his rather well-known *Organon of the Healing Arts,* in 1811 his *Pure Materia Medica,* and in 1828 his last work, the *Treatise on Chronic Diseases.* Homeopathy also became a fashionable approach to healing, and although it had no proven value, it was accepted by prominent lay people. Its advocates, like those of the Perkins tractors, accused the medical profession of being a "great confederation of bigoted monopolists."

The basis of homeopathy, was that "like cures like," and its materia medica was characterized by the enormous dilution of drugs to the billionth, trillionth, and indeed the decillionth degree. Homeopathic medical school continued in this country until the early 1900's, and there still exists in Philadelphia the Hahnemann Medical School, where, I understand, a one-hour lecture on homepathy is given every

fourth year, for economic reasons only. Homeopathy was regarded in 1860 much as we regard osteopathy now, and its adherents used many of the same arguments. (See Oliver Wendell Holmes' lectures on "Homeopathy and its Kindred Delusions," which are a pleasure to read, and, if one is involved in a debate on osteopathy, only too modern in their discussions.)

In 1874 another physician, Dr. Andrew Taylor Still, who apparently never finished his medical training, unhappy and perhaps resentful because his three children had died of cerebrospinal meningitis, developed the theory that disease is caused by maladjustment of the supporting tissues of the body, especially the spine. Although this theory underlies the practice of osteopathy, it has never been formally elaborated; indeed, as late as January 1957, a physiologist at the Kirksville College of Osteopathy stated that the definition of this concept was still a matter of personal interpretation.

To quote Dr. Still:

> "To administer drugs is to accuse God of incapacity. . . .
>
> "You may be sure the Divine Intelligence failed not to put into the machine of man a level by which to control fever. . . .
>
> "In my grief the thought came to me, that Deity did not give life simply for the purpose of so soon destroying it—such a Deity would be nothing short of a murderer. I was convinced there was something surer and stronger with which to fight sickness than drugs, and I vowed to search until I found it. The result was that, in 1874 I raised the flag of Osteopathy, claiming that 'God is God, and the machinery he put in man is perfect'. . . .
>
> "This is the first school which ever raised the flag on the globe, as far as history says, that God is Truth, and this can be proven. I can take His works and prove His perfection and he who takes his good old whisky and drugs, and says God is Perfection, is a liar. He who has lung fever, pneumonia, flux or any fever, and drinks his whisky, denies the whole idea of the perfection of God. He slaps it in the face, and not only that, but in effect says, God is a failure. . . .
>
> "In case of flux, when the bowels are on fire with pain an Osteopath presses the button of ease, and in a few minutes the agony is over and the child is hungry. . . .
>
> "Shame on the knife that cuts a woman like a Christmas hog. Almost one-half the women of today bear a knife-mark, and I tell you, God's intelligence is reproached by it. . . .

> "An Osteopath stands firm in the belief that God knew what to arm the world with, and follows His principles. And he who so far forgets God's teachings as to use drugs, forfeits the respect of this school and its teachings. God is the Father of Osteopathy, and I am not ashamed of the child of His mind."

The first school of osteopathy was chartered in 1892 and, although given the privilege of granting the M.D. degree, chose instead to grant the degree of Doctor of Osteopathy. Six schools of osteopathy still exist; all are privately supported, and none are affiliated with a university. At present osteopaths are given equal rights with Doctors of Medicine in 36 states, Minnesota being one of the twelve that limit their licenses. In Minnesota ostepaths are limited to the practice of manipulative therapy, minor surgery, obstetrics and the use of drugs in connection with minor surgery and obstetrics. Since nearly all babies are born in hospitals, osteopaths practice almost no obstetrics. Osteopathic schools now require three years of college before admission followed by four years of osteopathic medicine, and a year of internship. Certain academic colleges give credit for the first year in an osteopathic school as the fourth year of academic training and give a degree of Bachelor of Science upon its completion. In view of the facts that 36 states grant osteopaths unlimited licenses, that the armed services are now required to award them commissions, and that the Veterans' Administration is allowed to use their services, we must conclude that osteopaths, as well as physicians, are practicing medicine. But it should be noted that osteopathy is purely an American phenomenon; there are practically no osteopaths elsewhere.

Many years behind the osteopaths are the chiropractors. Their training period has increased from the original six months to the present four years. Chiropractic was originally osteopathy under a different name. To quote the definition of chiropractic, formulated by its apostles in endeavoring to secure the passage of a law permitting them to practice in New Jersey:

> "The term chiropractic when used in this act shall be construed to mean and be the name given to the study and application of a universal philosophy of biology, theology, theosophy, health, disease, death, the science of the cause of disease and art of permitting the restoration of the triune relationship between all attributes necessary to normal composite forms, to harmonious quantities and qualities by placing in juxtaposition the abnormal concrete positions of definite mechanical portions with each other by hand, thus correcting all subluxations of the articulations of the spinal column, for the purpose of permitting the re-creation of all normal cyclic currents through nerves

> that were formerly not permitted to be transmitted, through impingement, but have now assumed their normal size and capacity for conduction as they emanate through intervertebral foramina—the expressions of which were formerly excessive or partially lacking—namely disease."

If you listen to their radio interviews and read their newspaper advertisements, you must conclude that chiropractors also are practicing healing, even though it may not be termed medicine, and they, also, castigate the so-called bigoted monopolists of the medical profession.

So much for the various types of the practice of healing. My second point is that proper and legitimate influences are changing the practice of medicine, mostly beneficial, mostly necessary, and all in turn influenced either directly or indirectly by doctors of medicine. After graduation, the doctor's first contact with a regulatory body is with the State Board of Medical Examiners, which is composed entirely of physicians and is the only group that can grant a license to practice medicine. After that, outside influences appear on every side. The government also is involved in medical practice through the Food and Drug Administration, through Medicare, through the Treasury Department, the Narcotics Division, and other agencies.

The state government is also involved in the practice of medicine. The vast majority of mentally sick are in state hospitals. The feebleminded, the deaf and the blind have state institutions for their care. The State Board of Health is practicing mass health care—in inspecting water, milk, and food, in imposing quarantines, in setting up laboratories, etc. The Civil Defense Administration has plans which, naturally, take over all health care, public and personal, in the event of a major emergency. Practically all the indigent and the old people have medical care supplied by the Boards of Public Welfare, state and county, with added funds from the federal government. A similar list of medical services can be made for county and city agencies.

These governmental units are only part of the picture. The University and all the Colleges of the State also supply health services for their faculty, staff, and students. The school boards have school physicians. All private hospitals and most industries have health services or industrial physicians. Labor unions have had health and welfare clauses written into almost all labor contracts, or, like the Ladies Garment Workers and some of the machinists' unions, have their own clinics. In addition, there are the cooperative health plans such as

Kaiser Permanente Foundation in California and H.I.P. in New York, and the private health insurance companies, not to mention Blue Shield, which act to regulate fees. Hospitals and their staffs with requirements for standards, tissue committees, and medical audit committees surely regulate ways of practice, voluntary and uplifting, but regulating nevertheless. In clinic practice, not only do medical men regulate practice but the business manager also has his say. The lay health organizations: cancer, polio, heart disease, etc. as well as the hospital fund drives, all influence the practice of medicine.

In our complex civilization all these forces tend to grow in size and importance. Nonmedical people recognize this; they expect physicians also to recognize it, too, and to play their part in leadership and in guidance of all things concerned with life and health. Physicians have to recognize this responsibility of the profession and must be prepared to devote time and effort outside their strictly medical activities to fulfill this legitimate expectation of the public.

We have mentioned the deleterious influences of the irregular practitioner, and the regulating influence of outside forces on medicine, but now we must ask how we can maintain, from within, the high standards of the medical profession. It is a truism that the standard of a profession is determined by the standards of each of its members—in this case of the individual doctor whatever his role. The doctor's fundamental character is formed long before he comes to the medical school, but his professional standards and conduct are crystallized in medical school and in his internship. It is here that he must learn the fundamental dignity of the person, that statistics are a tool of research and hold cold comfort for the individual. All medicine is concerned with the welfare of the individual, and its practice ultimately must rest on an individual basis.

The persistence of cults results from the failure of individual physicians to fill the needs of individual patients, whether these needs be physical, emotional, or social. These needs are not fulfilled by a multiplicity of laboratory tests, they are not met through a sterile gauze curtain, nor by the application of computer techniques to electrocardiographic interpretation, nor by semi-automated diagnosis of heart disease as is now suggested. We need all the help possible from every source available, but we also need individual, person-to-person help. So far as people are concerned even sanitation is measured only in its effect on me, myself, not on statistics. After all, the profession of medicine is still a service; it is a communication between "I and Thou"

not between "I and It," whether the "It" be a laboratory procedure, a computer, or a statistic.

The World Medical Association in its Code of Ethics states that medicine as a profession cannot be practiced for money, although the physician can be paid for practice. That concept is one major difference between the physician and the cultist. As long as you can instill that concept in your students, as long as the practicing profession can maintain that idea, as long as the physician, wherever he is placed, in private practice, in politics, administration, or in governmental position can remember the dignity and the importance of the individual, then the integrity of the medical profession is safe.

Staff Meeting Report

Experimental and Clinical Studies on Adrenocortical Function in Shock Due to Infection*†

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Since the original reports of Waterhouse[1] and of Friderichsen,[2] secretory failure of the adrenal glands has continued to be implicated as a factor in the pathogenesis of peripheral circulatory collapse due to infection. Although the association of adrenal function and circulatory failure has been cited in recent reviews,[3,4,5] there has been no report of a deficit of adrenal secretory products or their urinary metabolites in peripheral collapse due to infection. This paper is concerned with assessing adrenocortical function and cortisol metabolism in human patients having peripheral circulatory failure due to severe infections, and in dogs following the production of shock by endotoxins of Gram-negative bacteria. Studies with a 21 hemisuccinate ester of cortisol, which is rapidly hydrolyzed to free cortisol *in vivo,* were undertaken in order to delineate the metabolism of cortisol, the principal adrenal secretory product in humans and in dogs.[6,7]

I. Studies on Adrenal Function and Cortisol Metabolism in Patients with Shock Due to Infection

The subjects of this study included nine healthy adults and 22 patients with severe infections complicated by circulatory collapse. All of these patients were hypotensive with systolic blood pressures under 90 mm. Hg. Fifteen of them had demonstrable bacteremia at the time of the studies.

Methods

Blood samples for the determination of cortisol concentrations in the plasma were analyzed by a modification of the method of Silber

*This report was given at the Staff Meeting of the University of Minnesota Hospitals on October 24, 1958.

†This investigation was supported in part by a grant from Merck & Co., Inc., Rahway, New Jersey.

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and Porter,[8] as described by Peterson, Karrer, and Guerra.[9] This method is specific for steroids with the 17, 21-dihydroxy-20-keto configuration, including cortisol, cortisone, Compound S, and their dihydro- and tetrahydro- derivatives. Of these, only cortisol exists in the plasma in significant concentrations; therefore, the method may be regarded as highly specific for cortisol.

Adrenal stimulation was carried out in eight normal subjects and in six patients with shock due to infection, by an intravenous infusion over a four-hour period of 25 U.S.P. units of corticotropin (Upjohn, Sterile Corticotropin Injection) dissolved in 500 ml. of 5 per cent dextrose in water. Specimens of 15 ml. of heparinized blood were secured before and after the infusion of corticotropin.

In order to determine the rate of disappearance of exogenous cortisol, an intravenous injection of 100 mg. of cortisol sodium succinate* dissolved in 2 ml. of distilled water (Upjohn, Hydrocortisone Sodium Succinate) was given to each of nine normal subjects and to 20 patients with shock. Samples of blood were obtained from all subjects immediately preceding the injection of cortisol sodium succinate, and from the patients with shock at 30, 90, 150, 210, and 270 minutes thereafter.

Results

A. Relationship of the Clinical Status to the Outcome

Demonstrable bacteremia was associated with shock in 70 per cent of the cases, Gram-negative bacteria being most frequently isolated. The severity of the underlying infectious process is emphasized by the fact that staphylococci were isolated from the blood in 50 per cent of those who died. In the nine autopsies performed in the series, no adrenal pathologic change could be demonstrated, except in one patient, who had had a hematoma in a single adrenal gland. A characteristic difference between the appearance of those who died and the appearance of those who recovered was frequently recorded: The skin of the patients who died was often ashen gray, cold, and moist, with mottling and cyanosis such as is encountered in severe hemorrhagic shock, while the survivors had suffused, warm skin and a full pulse in the presence of hypotension. This dichotomy in the clinical picture of shock has been reported by Waisbren[10] and by Hall and Gold.[11] The two groups differed significantly as to duration of hypotension; while the patients who recovered were hypotensive for an

*The cortisol 21-hemisuccinate ester was generously supplied by the Upjohn Co., Kalamazoo, Mich., through the courtesy of Dr. C. J. O'Donovan.

average of 23 hours, the patients who died were hypotensive for an average of six to seven days. All patients were considered to be hypotensive until they no longer required pressor substances for the maintenance of blood pressure.

B. Concentration of Cortisol in the Plasma

In the healthy subjects the concentrations of plasma cortisol averaged 13 μg/100 ml, with a range of 7 to 22 μg/100 ml. The mean plasma cortisol concentration of patients with shock due to infection was 63 μg/100 ml, ranging from 30 to 160 μg/100 ml. Moreover, for the patients in shock the mean plasma cortisol concentration was higher at the outset than it was for normal subjects after a four-hour infusion of corticotropin; in only one patient with shock was the plasma cortisol level within the normal range.

C. Effect of an Intravenous Infusion of Corticotropin on Plasma Cortisol Concentrations

Four-hour intravenous corticotropin tests were performed on eight normal individuals. The mean control value for cortisol was 15 μg/100 ml of plasma, with a range of 5 to 24μg/100 ml. Following the infusion of corticotropin, the concentrations rose to a range of 32 to 63 μg/100 ml, with a mean of 46 μg/100 ml.

Four-hour corticotropin tests were also carried out in six patients with shock. The initial plasma cortisol levels averaged 53 μg/100 ml and ranged from 36 to 76 μg/100 ml. After a four-hour infusion of corticotropin these levels rose to an average of 100 μg/100 ml of plasma, with a range of 81 to 119 μg/ 100 ml. Three patients, all of whom died, had had average post-corticotropin infusion levels of 112 μg/100 ml of plasma; whereas the mean value in the three patients who recovered was 88 μg/100ml. Urinary 17-hydroxycorticosteroids were not determined in this study because nearly all the patients were oliguric, and azotemia rapidly developed in some. While the excretion of urinary 17-hydroxycorticosteroids is usually a valuable index of cortisol production, in shock, when a reduction in urinary output is coupled with retention of conjugated cortisol metabolites in the plasma, the results of such determinations are unreliable.

D. Mean Biological Half-time of Infused Cortisol Sodium Succinate in the Plasma

It was mentioned that the mean initial plasma concentrations of cortisol in all the patients were significantly elevated compared to the values found in the normal subjects. Moreover, the initial levels in the patients who died were higher than those in the patients who survived. The mean biological half-time of cortisol in normal subjects was 101.6

minutes; in patients who recovered, this value was 95.1 minutes; and in those who died, 468.2 minutes. The biological half-time of cortisol in the plasma is determined to a large extent by the functional integrity of the liver.[12] Liver function tests performed in six of the moribund patients showed abnormal function in all six. Liver function in four of the surviving patients was found to be normal. The half-time values of plasma cortisol in the healthy subjects were not significantly different from those in the patients who survived.

Summary

1. Adrenal function was studied in healthy adults and in 22 adult patients having shock due to infection. Three quantitative studies were employed: First, the basal plasma cortisol level was determined. Second, the response of the adrenal gland to stimulation with corticotropin was measured in terms of change in plasma cortisol concentration. Third, the biological half-time of exogenous cortisol injected as the succinate ester in plasma was evaluated.

2. All the patients with shock had considerably higher basal concentrations of cortisol in the plasma than did the healthy subjects. In six patients with shock who were studied there was a response to corticotropin similar to that obtained in the healthy adults. The biological half-time of exogenous cortisol in those patients with shock who survived was not different from that in healthy subjects, but in those who died the biological half-time was considerably longer than that observed in healthy subjects.

3. Accelerated adrenal secretory activity was demonstrated in those patients who survived. In moribund patients unequivocal proof for increased adrenal secretory activity could not be obtained.

II. Effects of Endotoxin in Dogs on the Secretion And Metobalism of Cortisol

In the human patients with severe infections complicated by circulatory collapse described earlier in this report, peripheral blood levels of cortisol were elevated. The significance of an elevated plasma level of cortisol cannot be assessed without information on the rate of removal of the steroid from the plasma or on the rate of adrenal production. Urinary metabolites of cortisol may reflect adrenal secretion, but the measurements are subject to wide error under conditions of altered renal and hepatic function.[12] Responsiveness to corticotropin as measured by changes in the concentration of plasma cortisol suggests continued integrity of adrenocortical function, but for reasons

already cited, it does not indicate the magnitude of the response in patients having shock due to infection. In an attempt to secure this information, the cortisol in the adrenal venous blood of dogs was measured after the animals had been subjected to endotoxin shock. Insertion of a cannula into the lumbo-adrenal vein of the dog with collection of the total adrenal venous effluent provides a direct and specific method for evaluating adrenal secretory activity.

It has been established that a single injection of a large dose of endotoxin into mature experimental animals regularly results in fever, shock, and death.[13] Weil and his associates[14] have shown that an intravenous injection of endotoxin into the dog is followed by a predictable and reproducible sequence of events. Therefore, since the experimental conditions were reproducible and adrenal secretory activity could be measured directly, the assessment of the effect of endotoxins on adrenocortical function was carried out in the adult dog.

Materials and Method

Sixty-eight adult mongrel dogs ranging from six to 26 kilograms in weight were used in this study. All were anesthetized with pentobarbital sodium (30 mg/Kg) before being subjected to experimental procedures. A permanent polyethylene cannula was placed in the right lumbo-adrenal vein of each of 40 dogs, according to a technique described by Hume and Nelson.[15] This preparation permits either continuous or intermittent collection of the total venous effluent of the right adrenal gland. Adrenal venous blood was collected for five-minute periods at varying intervals, following which each cannula was filled with 4 per cent heparin in physiological saline solution. Experiments were carried out 18 to 24 hours after the cannula had been inserted. Peripheral blood specimens, obtained from the femoral vein by means of a small-gauge polyethylene catheter, were analyzed for cortisol as described above.

Purified endotoxin of the Boivin type, derived from *E. coli* and prepared by the method of Spink and Anderson,[16] was administered to five dogs in a dosage of 1.9 mg. per Kg., a single injection uniformly producng profound shock and eventually death. In 12 dogs a nonlethal lipopolysaccharide derived from *Salmonella abortus equi* (Pyrexal®)* was administered intravenously in a dose of 0.002 mg.; this did not produce shock but did cause a pyrogenic reaction.

*Supplied by the Wander Co., Chicago, through the courtesy of Dr. Fred H. Schultz

Experimental Procedure

1. After collection of a single sample of adrenal venous blood, each of seven dogs received a lethal dose of *E. coli* endotoxin injected intravenously. Adrenal venous effluent was collected at 30 and 120 minutes following the injection. The specimens of adrenal venous blood were then analyzed for cortisol concentration, and the output of cortisol from the right adrenal gland was calculated by this simple formula:

$$\frac{\text{Cortisol in micrograms/ml of plasma} \times \text{Adrenal venous blood flow rate in ml/min.}}{\text{2 (assuming the hematocrit level to be 50\%)}} = \text{Output in micrograms/min.}$$

After control specimens were obtained, an injection of 0.002 mg. of endotoxin (Pyrexal) was given each of another six dogs, and subsequent samples of blood—collected from the adrenal vein at 5, 30, 60, 120, and 180 minutes—were treated as described above. A rapid single injection of 25 U.S.P. units of corticotropin (Upjohn, Sterile Corticotropin Injection) was given to each of three dogs after a control sample had been obtained via the cannula in adrenal vein. Specimens collected at 30, 60, 90, 120, and 180 minutes after the corticotropin injection were treated as above.

2. Ten dogs with adrenal vein cannulas were rapidly given a single injection of 15 U.S.P. units of corticotropin after control specimens were obtained. Samples of blood from the adrenal vein were taken at 5, 10, and 120 minutes after the injection. Within the next 30 minutes a lethal dose of *E. coli* endotoxin was administered in a single injection, and blood was collected from the adrenal vein 5, 60, 120, and 180 minutes afterward. At 185 minutes after the administration of endotoxin, a second injection of corticotropin was given, and samples were taken at 5 and 10 minutes. This same procedure was followed in seven dogs a few hours after they had been hypophysectomized transtemporally.[17] Another seven dogs were given a constant infusion of corticotropin in physiological saline solution at the rate of 0.3 U.S.P. units/min. Specimens of blood from the adrenal vein were collected hourly for three hours; within the next 30 minutes a lethal dose of endotoxin was administered intravenously, and samples were obtained at five minutes, and one, two, and three hours thereafter.

3. In order to determine the rate of removal of exogenous cortisol from the plasma, an intravenous injection of cortisol as the succinate ester dissolved in 2 ml. of distilled water (Upjohn, Hydrocortisone

Sodium Succinate) was given in a dosage of 5 mg/Kg to ten normal anesthetized dogs; to six dogs following an injection of a pyrogenic dose of endotoxin (0.002 mg.); and to seven dogs who had received lethal doses of *E. coli* endotoxin (1.0 mg/Kg) intravenously. Samples of peripheral (femoral) venous blood were obtained immediately preceding the injection of the cortisol sodium succinate and at 30, 60, 90, 120, and in some at 180 minutes thereafter. Plasma cortisol concentrations were determined as described.

Results

A. Adrenal Secretory Response to Pyrogenic and Lethal Doses of Endotoxin Compared with the Response to Exogenous Corticotropin

The basal output of cortisol in all the animals averaged less than one μg/min. Thirty minutes after the injection of corticotropin the output rose to a mean of 8.1 μg/min, with a range of from 7.3 to 9.3 μg/min. After this single injection of corticotropin (25 U.S.P. units) the values remained elevated at 120 minutes with a mean output of 11.0 μg/min and a range of 7.5 to 13.2 μg/min, and they decreased thereafter. In subsequent experiments using smaller doses of exogenous corticotropin, maximal adrenal secretory responses were of shorter duration. In general, the duration of increased adrenal cortisol secretion was directly related to the administered dose of corticotropin. Following a lethal dose of endotoxin, adrenal secretion of cortisol rose to an average of 8.9 μg/min, with a range of from 4.1 to 15.7 μg/min; 120 minutes after the injection of endotoxin, cortisol output rose further to 9.6 μg/min with a range of from 6.0 to 17.4 μg/min. Thus the adrenal secretory response to a lethal dose of endotoxin was of the same order of magnitude as the response to a large dose of exogenous corticotropin.

The injection of a pyrogenic dose of endotoxin, which resulted in neither hypotension nor death, increased the output of cortisol but to a lesser extent than did a lethal dose of endotoxin or exogenous corticotropin. The average maximum value of 8.9 μg/min with a range of from 4.0 to 11.2 μg/min was achieved within 60 minutes after injection, both the rise and the decline being more gradual. Five minutes after the injection of the pyrogen, significant increases in cortisol secretion occurred in only two of the six animals tested, but by 30 minutes, four of the dogs demonstrated a rise in cortisol output. During this period the rectal temperature increased an average of 0.6° C., but correlation between cortisol output and fever was erratic, and in two dogs large increments in cortisol production *preceded* changes in rectal temperature.

B. Influence of Lethal Doses of Endotoxin on the Response of Adrenal Secretion to Exogenous Corticotropin in Intact and in Hypophysectomized Dogs

1. Intact Animals

In the intact animals the response to the same dose of corticotropin five minutes after injection varied from 4.0 to 17.3 μg/min, with an average cortisol output of 9.5 μg/min. Two collections at five and ten minutes following corticotropin were found adequate to encompass maximal responses in most of the animals tested. The cortisol output fell toward the baseline levels after two hours to a mean value of 4.4 μg/min, with a range of from 1.0 to 10.8 μg/min. It should be recalled that in dogs given a larger dose of corticotropin (25 U.S.P. units) in the initial experiments, the output of cortisol continued at a maximum throughout this period. A longer interval between the administration of corticotropin and the injection of endotoxin would have been necessary had the dose of corticotropin not been reduced to 15 units.

In general, the response to a lethal dose of endotoxin was of the same order of magnitude as that for corticotropin. Thus, five minutes after the injection of endotoxin, when the dogs were hypotensive and hyperpneic, the mean cortisol output was 9.1 μg/min, with a range of from 2.4 to 28.3 μg/min. Three hours following this injection the dogs were hypotensive and febrile, but cortisol output had declined to an average of 7.3 μg/min with a range of 2.3 to 12.0 μg/min. Two of the ten animals studied died by the end of this period. In one dog who died, the cortisol output from the right adrenal gland was 5.3 μg/min five minutes before death. In another animal who died within ten minutes following the collection of the two-hour specimen, this value was 6.8 μg/min. In the surviving eight animals, corticotropin produced a small but definite rise in adrenal cortisol output; this increment was shortlived, lasting only five minutes. These experiments indicate that although the adrenal secretion of cortisol is well above baseline values three hours after the injection of a lethal dose of endotoxin, there is a definite attenuation of responsiveness to exogenous corticotropin.

2. Hypophysectomized Animals

Further definition of the degree of change in adrenal secretory activity in response to corticotropin following endotoxin shock was attempted in the experiments using hypophysectomized dogs. Experiments on these dogs were carried out within 3 to 24 hours following hypophysectomy. The response of these animals to corticotropin was

less pronounced than that of the intact dogs; maximum mean output of cortisol of 7.5 μg/min with a range of from 3.2 to 17.2 μg/min was reached ten minutes after the injection of corticotropin. Cortisol output did not rise during the three hours following the injection of endotoxin. On the basis of these data, endotoxin does not appear to stimulate adrenal secretory activity directly. The magnitude of response to corticotropin after endotoxin was greatly diminished in the hypophysectomized animals, the average maximum response being 2.4 μg/min with a range of from 1.0 to 3.7 μg/min.

3. Constant Infusion of Corticotropin in Intact Animals

The effect of endotoxin on adrenal cortisol output in response to exogenous corticotropin was also assessed by means of a prolonged constant infusion of large amounts of corticotropin at a rate of 0.3 units per minute continued for seven hours. By the end of the third hour, cortisol output averaged 15.4 μg/min. A lethal dose of endotoxin was injected during the infusion of corticotropin. One hour following the endotoxin injection the output of cortisol dropped to 11.3 μg/min, even though the infusion of corticotropin was continued. Adrenal cortisol output fell progressively, reaching an average of 8.3 μg/min within three hours after the endotoxin had been given. One animal died immediately following collection of a specimen one hour after the endotoxin injection; the dog's cortisol secretion was 10.1 μg/min just prior to death. Another dog succumbed 30 minutes following the collection of a specimen two hours after the administration of endotoxin, and the cortisol output just before death was 3.6 μg/min.

C. Concentration of Cortisol in the Peripheral Venous Plasma in Dogs Following Injections of Pyrogenic or Lethal Doses of Bacterial Endotoxins

Thirty minutes after the injection of either pyrogenic or lethal doses of endotoxin, plasma cortisol rose significantly. No appreciable difference was observed in either group of dogs, suggesting that the main independent variable affecting plasma cortisol concentration was increased adrenal secretory activity.

D. Biological Half-times of Cortisol in the Plasma when Infused as the Succinate Ester

The mean biological half-time of cortisol in the plasma calculated from the plasma levels after an infusion of cortisol may be used as an index of the metabolic disposal of cortisol. This half-time value was 56.6 minutes in the control animals, 40.1 minutes in dogs given only pyrogenic doses of endotoxin, and 116.6 minutes in those given lethal

doses of endotoxin. The half-time value for cortisol in the plasma is determined to a large extent by the functional integrity of and blood flow to the liver.[12] The intense congestion and stasis of blood in the livers of dogs following lethal doses of endotoxin has been described.[14] Thus, elevated levels of cortisol in the plasma of dogs after the production of endotoxin shock may be due in large part to impaired disposal of cortisol.

Summary

1. Injection of endotoxins of Gram-negative bacteria in pyrogenic and lethal doses produced a rapid increase in adrenal secretory activity, determined by the direct measurement of cortisol in the effluent of the cannulated right lumbo-adrenal vein of the dog. This response to endotoxin was of the same order of magnitude as the adrenal secretory response to stimulation by exogenous corticotropin.

2. The adrenal secretory response to exogenous corticotropin in dogs was diminished following the injection of a lethal dose of endotoxin.

3. Increased adrenal secretion of cortisol in response to injected endotoxin was abolished in hypophysectomized dogs.

4. The concentration of cortisol in the peripheral blood rose significantly in animals given either pyrogenic or lethal doses of endotoxin.

5. The biological half-time of exogenous cortisol in the plasma of dogs following a pyrogenic dose of endotoxin was rapid, and in dogs following a lethal dose of endotoxin, prolonged. Therefore, the elevated levels of plasma cortisol in the dogs that received a pyrogenic dose of endotoxin is due solely to increased adrenal secretory activity. In the dogs that received a lethal dose of endotoxin, increased concentrations of cortisol in the plasma are due in part to increased adrenal secretion of cortisol and in part to retarded removal of cortisol from the plasma.

III. The Protection by Cortisol Against the Damaging Effects of Endotoxin

In the experiments described above it was not possible to demonstrate secretory failure of the adrenal glands in the dog after lethal doses of endotoxin, or in the human with circulatory collapse due to infection. Protection against the lethal effect of bacterial endotoxins by pre-treatment with cortisol and its analogs has been demonstrated in various mammalian species.[4,16] In these experiments such protection was accomplished by doses of steroid hormones far exceeding the

amount the particular experimental animal was capable of producing endogenously. Inferences that beneficial effects of adrenocortical substances in a given situation provide evidence of adrenal insufficiency are unwarranted.

The mechanism of the protective action against the lethal effect of endotoxin by cortisol is unknown. Although cortisol does not prevent shock due to endotoxin in the dog, it does significantly reduce mortality.[18] The activity of glutamic oxalacetic transaminase in the serum provides a sensitive but nonspecific index of cellular injury in cardiac and skeletal muscle, and in renal and hepatic tissues.[19] Watson[20] found a rise in serum transaminase activity in rabbits following intravenous administration of streptococcal toxin. In the present experiments, the level of serum oxalacetic transaminase as an index of tissue injury was studied to determine: (1) the degree of tissue injury produced by endotoxins of Gram-negative bacteria, and (2) the effectiveness of exogenous cortisol in preventing tissue injury by endotoxin.

Procedures

A. Serum Transaminase Activity after a Sublethal Dose of E. Coli Endotoxin

Ten adult mongrel dogs (12.0 to 16.6 Kg.) were used. A blood sample was obtained from each just prior to the intravenous injection of 0.05 mg/Kg of *E. coli* endotoxin, and another blood specimen was taken two hours later. The sera were separated from the red cells by centrifugation and frozen until glutamic oxalacetic transaminase determinations were made by the method of Karmen *et al.*[21]

B. Lethal Doses of Endotoxin in Dogs having Adrenal Vein Cannulas

Eleven dogs (9.2 to 23.7 Kg.) were used in this experiment. A polyethylene catheter was placed in the right lumbo-adrenal vein of each as described previously. Samples of peripheral and adrenal venous blood were obtained prior to, 30 minutes after, and two hours after the intravenous injection of *E. coli* endotoxin in a dose of 1 mg/Kg. Peripheral blood samples were used for transaminase determinations, and analyses for cortisol were made on timed blood samples from the adrenal vein. Minute cortisol outputs were calculated as described.

C. Lethal Doses of Endotoxin in Intact Dogs

Twelve dogs (6.0 to 18.2 Kg.) were used. Peripheral blood samples were obtained for transaminase and cortisol determinations prior to,

and 30 minutes, two, four, and six hours after the intravenous injection of *E. coli* endotoxin (1 mg/Kg).

D. Lethal Doses of Endotoxin in Intact Animals Given Intravenous Cortisol

Six dogs (9.0 to 17.0 Kg.) were used. An intravenous injection of 100 mg. of cortisol as the succinate ester dissolved in 2 ml. of distilled water was given to each after blood samples were obtained. An intravenous infusion of 200 mg. of cortisol free alcohol dissolved in 500 ml. of 5 per cent dextrose in distilled water was begun and regulated to deliver 0.6 mg. of cortisol per minute throughout the experiment. *E. coli* endotoxin (1 mg/Kg) was injected intravenously. Blood specimens were drawn at 30 minutes and at two, four, and six hours.

Results

A. Effect of Sublethal Doses of Endotoxin on Transaminase Activity

All test animals survived, and all had febrile responses within an hour of administration of endotoxin.

The control transaminase value rose from a mean activity of 22 units/ml of serum (Range=10-32 units/ml) to a mean activity of 82 units/ml of serum (Range=57-131 units/ml). This rise suggests that sublethal doses of endotoxin produces a significant degree of tissue injury.

B. Lethal Doses of Endotoxin in Dogs with Adrenal Vein Cannulas

The serum transaminase values rose from a pre-endotoxin control level of 16.6 units/ml (Range=10-28 units/ml) to a mean of 192.4 units/ml (Range=108-357 units/ml) in 2 hours. This rise is significantly higher than the rise recorded for dogs who received sublethal doses of endotoxin. Transaminase activity at 30 minutes was clearly elevated, with a mean value of 50.8 units/ml (Range=18-99 units/ml). All animals died within 24 hours after the injection of endotoxin.

The minute output of cortisol from the adrenal vein rose from a mean of 1.0 μg/min (Range=0.4-2.5 μg/min) to a maximum of 9.6 μg/min (Range=6.0-17.4 μg/min).

C. Lethal Doses of Endotoxin in Intact Animals

Eleven of the 12 dogs died within 24 hours after endotoxin was administered. The mean control value for transaminase activity was 22.1 units/ml of serum (Range=10-35 units/ml). The highest level of transaminase activity was found at the sixth hour, with a mean of 504.1 units/ml of serum (Range=186-1080 units/ml). The mean value at two hours was 236.3 units/ml of serum in this group, whereas in the dogs given sublethal doses of endotoxin, the mean value was

only 82 units/ml of serum. A direct relationship may exist between dose of endotoxin and degree of tissue injury. The plasma cortisol values rose from a mean control of 14 μg/100 ml of plasma to a mean of 57 μg/100 ml of plasma at six hours. The post-endotoxin blood cortisol levels are similar to those obtained after stimulation with corticotropin. This is in agreement with the observed increased adrenal secretory activity due to endotoxin in the dogs having adrenal vein cannulas.

D. Lethal Doses of Endotoxin in Intact Animals Given Infusions of Cortisol

Three of the six dogs in this group survived lethal doses of endotoxin. Although the number of animals is not large enough to justify definitive conclusions, the increased survival suggests that cortisol protects to a variable degree against the lethal effect of endotoxin.

In the presence of extremely high concentrations of cortisol in the blood, the transaminase levels rose from a mean of 25.6 units prior to the injection of endotoxin to a mean of 120.6 units six hours later. This value was less than one-fourth of that obtained in the dogs who received endotoxin alone. While the transaminase levels in the dogs receiving only endotoxin reached a twenty-fivefold increment over control levels, in the dogs treated with cortisol, endotoxin produced less than a fivefold increment. The concentration of plasma cortisol in the treated group varied from 600 to 2,000 μg/100 ml. More often than not, cortisol concentration in the plasma was inversely related to transaminase activity.

Conclusions

1. Secretory failure of the adrenal glands could not be demonstrated in human patients with circulatory collapse due to severe infection or in dogs after lethal injections of endotoxins derived from Gram-negative bacteria. Conversely, it was possible to demonstrate increased secretory activity of the adrenal glands in patients with shock due to infection and in dogs made hypotensive with endotoxin.

2. The results of these experiments suggest that cortisol exerts a protective effect against the lethal and tissue-injuring effects of bacterial endotoxins when used in pharmacologic doses. For reasons stated above, the protection afforded by cortisol when administered in supraphysiologic amounts cannot be regarded as "replacement" therapy.

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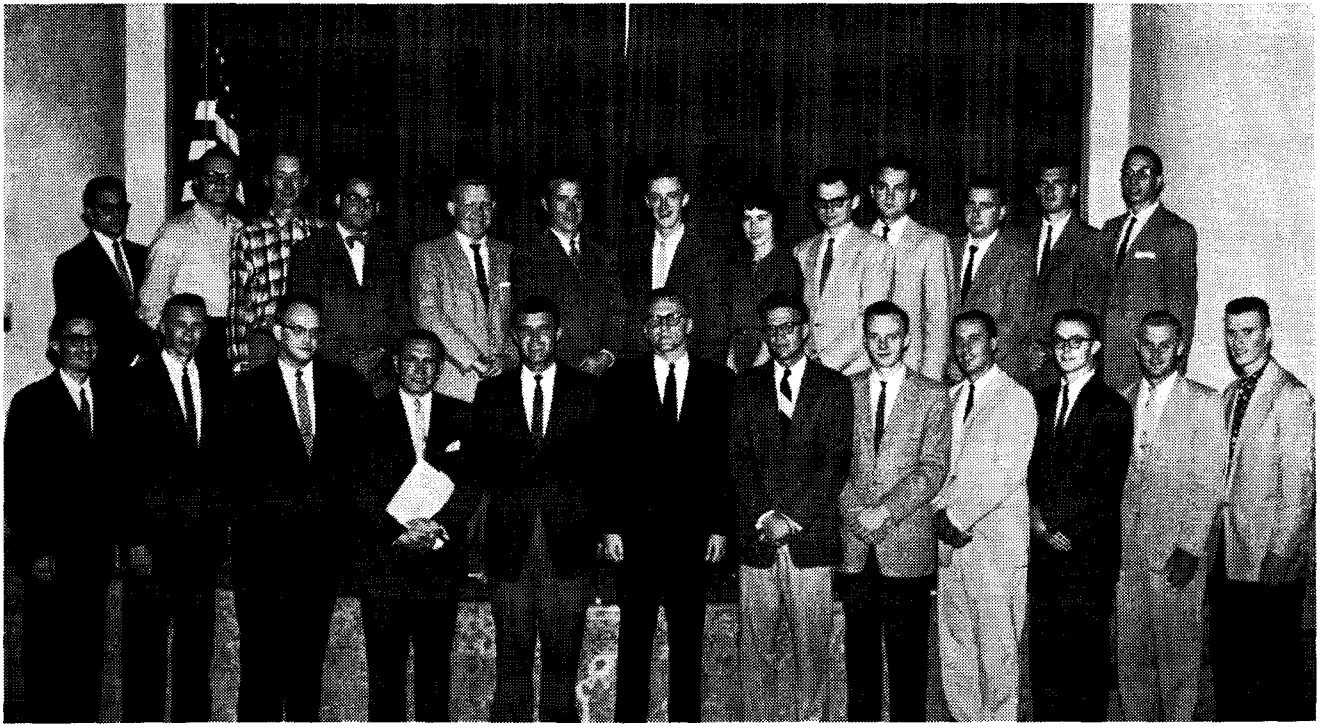
MINNESOTA MEDICAL FOUNDATION SCHOLARSHIP RECIPIENTS



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Editorial

The Hidden Scholarship

On the opposite page there is a photograph of the recipients of the Minnesota Medical Foundation Scholarships for the current year. We congratulate these students for having demonstrated ability sufficiently outstanding that they be recognized as worthy of receiving scholarships to aid them in their studies in the Medical School. Likewise, we congratulate the members of the Minnesota Medical Foundation for their foresight in planning a program of assisting worthy students by awarding scholarships to them.

We would be quite remiss, however, if we did not comment on the scholarship awarded *every* student in the Medical School, because there is a "hidden scholarship" given to each medical student which provides financial aid over and above the tuition and fees paid by him, and which has been estimated to be approximately five times the total amount paid by any student during his four years in the Medical School. The present costs of obtaining a medical education are quite great, but it is easy to see that if each student were forced to pay for the *total* cost of his education, then only a small minority of the present students would be able to attend, and thus the continuing supply of physicians would be interrupted.

How is this hidden scholarship paid for? By the taxpayers of the state in the form of direct aid to the University; by the federal government in many indirect ways, such as grants from the Department of Health, Education, and Welfare; by the many voluntary health agencies which offer grants and scholarships; by many pharmaceutical firms throughout the country; by the interest from endowment funds in the Medical School; and last, and perhaps most important, by those individual physicians with a sense of moral obligation to the advancement of knowledge who personally make financial contributions to the field of medical education. These physicians are repaying, in the strictest sense, part of the hidden scholarship which *they* received during their own medical education. By this means they offer encouragement and support to present students, and thereby aid in assuring the continuing supply of physicians.

We may look for funds from all of the above agencies, but none the less we as individuals must ourselves accept most of the responsi-

bility for insuring a supply of physicians. It remains, therefore, for each of us to re-examine the hidden scholarships that he received during his period of education and then evaluate what he as an individual can do to repay this scholarship and enable the Medical School to continue its work in the teaching and training of future physicians;—*"Therefore never send to know for whom the bell tolls: It tolls for thee."*

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WEEKLY CONFERENCES OF GENERAL INTEREST

Physicians Welcome

Monday,	9:00 to 10:50 A.M.	OBSTETRICS AND GYNECOLOGY Old Nursery, Station 57 University Hospitals
	12:30 to 1:30 P.M.	PHYSIOLOGY- PHYSIOLOGICAL CHEMISTRY 214 Millard Hall
	4:00 to 6:00 P.M.	ANESTHESIOLOGY Classroom 100 Mayo Memorial
Tuesday,	12:30 to 1:20 P.M.	PATHOLOGY 104 Jackson Hall
Thursday,	11:30 A.M. to 12:30 P.M.	TUMOR Todd Amphitheater University Hospitals
Friday,	7:45 to 9:00 A.M.	PEDIATRICS McQuarrie Pediatric Library, 1450 Mayo Memorial
	8:00 to 10:00 A.M.	NEUROLOGY Station 50, University Hospitals
	9:00 to 10:00 A.M.	MEDICINE Todd Amphitheater, University Hospitals
	1:30 to 2:30 P.M.	DERMATOLOGY Eustis Amphitheater University Hospitals
Saturday,	7:45 to 9:00 A.M.	ORTHOPEDICS Powell Hall Amphitheater
	9:15 to 11:30 A.M.	SURGERY Todd Amphitheater, University Hospitals

For detailed information concerning all conferences, seminars, and ward rounds at University Hospitals, Ancker Hospital, Minneapolis General Hospitals, and the Minneapolis Veterans Administration Hospital, write to the Editor of the BULLETIN, 1342 Mayo Memorial, University of Minnesota, Minneapolis 14, Minnesota.