

THE FUTURE OF ANTALGESIC THERAPY

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THE DISTINGUISHED AMERICAN STATESMAN, SAGE, AND THE THIRD PRESIDENT OF THE UNITED STATES OF AMERICA, THOMAS JEFFERSON, WROTE ONE TIME, "THE ART OF LIFE IS THE ART OF AVOIDING PAIN."

THE ATTENTION TO THE PROBLEM OF PAIN BY MANY OF US IS REQUIRED. WHEN PAIN BECOMES A DISEASE, IT DOES SO WHEN THE BASIC ILLNESS CAUSING PAIN IS OUT OF CONTROL. THE WHOLE ART OF LIVING IS THEN TOTALLY CONDITIONED BY THE ABILITY TO CONTROL THE PAIN.

THERE ARE MANY APPROACHES FOR THE DISCUSSION THAT I HAVE PLANNED, BUT IN THE PRESENCE OF OUTSTANDING EXPERTS IN VARIOUS ASPECTS OF THE BIOLOGY AND TREATMENT OF PAIN, I BELIEVE IT IS MOST USEFUL FOR ME, AND HOPEFULLY FOR YOU, THAT I SHOULD BE ABLE TO CONCENTRATE ON ONLY ONE VERY IMPORTANT ASPECT OF THE PROBLEM OF PAIN. I HAVE ELECTED TO DEAL ENTIRELY WITH A MOST IMPORTANT AND HELPFUL APPROACH TO PAIN THERAPY THAT WAS DEVELOPED BY MY FRIEND, AND THE COLLEAGUE OF ALL OF US, PROFESSOR GUIDO MORICCA.

MORICCA APPROACHED THE SUBJECT FROM THE STANDPOINT OF AN ANESTHESIOLOGIST WHOSE RESPONSIBILITIES WERE TO DEAL WITH PATIENTS WITH CANCER. IT SOON BECAME APPARENT TO HIM AND HIS COLLEAGUES THAT PROVIDING ANESTHESIA FOR THE SURGICAL TREATMENT OF CARCINOMA WAS FAR FROM

ADEQUATE. IT BECAME INCREASINGLY OBVIOUS IN HIS LARGE AND IMPORTANT CLINIC FOR CANCER RESEARCH IN ROME THAT THE PAIN DUE TO CANCER IS, AS HE DESCRIBED IT "MULTIPLE, DIFFUSE, NOT WELL LOCALIZED AND, THEREFORE, UNTREATABLE; IT THEN BECOMES THE DOMINANT SUBJECT DEVELOPMENT IN THE CLINICAL SYMPTOMATOLOGY." THE DIFFUSE NATURE OF THE PAIN AND THE VAST IMPORTANCE OF IT IS ALSO A CRITICAL PROBLEM IN THE UNITED STATES OF AMERICA WHERE CANCER IS THE SECOND LARGEST CAUSE OF DEATH AND THE HORRORS OF THE PAIN SYNDROME THAT THESE PATIENTS SUFFER IS VERY SERIOUS INDEED.

IN 1963 THE OBSERVATION WAS MADE BY MORICCA THAT PAIN DUE TO HORMONAL DEPENDENT TUMORS CAN BE ALLEVIATED BY HORMONE TREATMENT, EITHER ADDITIVE OR SUBTRACTIVE. THE WELL KNOWN RELIEF OF PAIN FROM CARCINOMA OF THE PROSTATE WHICH IS HORMONAL DEPENDENT BY ORCHIECTOMY WAS AN EARLY DEMONSTRATION OF THIS FACT OF BIOLOGY. STUDIES IN EUROPE AND IN THE UNITED STATES INDICATED THAT REMOVAL OF THE ADRENAL GLANDS, THE OVARIES, AND EVEN THE PITUITARY GLAND SEEM TO BE PRODUCTIVE WAYS OF DEALING WITH THE CONTROL OF CANCERS WITH HORMONAL DEPENDENCE AND PERHAPS ALSO TO THE PAIN THAT THE CANCER PRODUCED. THE SUPPRESSION OF THE PITUITARY FUNCTION FOR THE PURPOSE OF ALLEVIATING PAIN WAS, IN THE PATIENTS WE ARE DISCUSSING, A

FORMIDABLE RISK WHEN IT WAS BEGUN SOME TWENTY-FIVE OR SO YEARS AGO IN SEVERAL COUNTRIES THROUGHOUT THE WORLD. SURGICAL ACCESS TO THE PITUITARY INVOLVED CRANIOTOMY AND THE MORTALITY RATE, WHILE ACCEPTABLE CONSIDERING THE PROBLEMS INVOLVED, WAS CLEARLY NOT THE WAY IN WHICH SUBSTANTIAL NUMBERS OF PATIENTS HAVING PAIN COULD OR SHOULD BE TREATED. THE OBVIOUS TECHNICAL LIMITATIONS FOR SURGICAL ABLATION OF THE PITUITARY, AND THE UNDESIRABILITY OF SUBJECTING THESE PEOPLE TO SERIOUS SURGERY, SUGGESTED TO MORICCA AND HIS ASSOCIATES THAT, IF POSSIBLE, A NON-SURGICAL METHOD TO DESTROY THE PITUITARY SHOULD BE DEVELOPED.

IN THE DAYS WHEN SUCH APPROACHES WERE BEGUN, RELATIVELY UNSOPHISTICATED LOCALIZATION TECHNIQUES FOR RADIATION THERAPY WERE AVAILABLE AND, IN FACT, THEY DID NOT WORK OUT WELL. THE COLLATERAL DAMAGE TO OTHER NEURAL ELEMENTS AND PARTS OF THE BRAIN, AMONG OTHER REASONS, WAS A LIMITING FACTOR.

THE DESTRUCTION OF THE PITUITARY BY OTHER METHODS SUCH AS MARKED REDUCTION IN TEMPERATURE, MARKED ELEVATION IN TEMPERATURE, OR BY ULTRASOUND ALSO ARE LIMITED. THE IMPLANTATION OF RADIOACTIVE MATERIALS AT THAT TIME POSED OTHER PROBLEMS. THE DESTRUCTION OF THE PITUITARY GLAND, THEREFORE, HAD TO BE PERFORMED BY

ANOTHER MODALITY AND THE METHOD THAT MORICCA DEVELOPED OF DESTROYING THE PITUITARY BY A TRANSNASAL INJECTION OF ABSOLUTE ALCOHOL INTO THE FLUID IN SITU IN THE SELLA TURCICA WAS DECIDED UPON. THE PROBLEM WAS ONE OF DEVELOPING A TECHNIQUE WHERE NEEDLES COULD BE PLACED SAFELY AND PRECISELY INTO THE PITUITARY GLAND ITSELF.

WITH THE SKILLFUL USE OF RADIOLOGICAL TECHNIQUES BEGINNING IN 1963 AND REFINED AT INTERVALS SINCE THEN, CHEMICAL DESTRUCTION OF THE PITUITARY GLAND WAS INTRODUCED INTO CLINICAL PRACTICE AND BECAME A SUBJECT OF VAST IMPORTANCE IN THE MANAGEMENT BOTH OF PAIN DUE TO CANCER AND THE CANCER ITSELF. VARIOUS ANALGESIC AND ANESTHETIC METHODS WERE EMPLOYED AND THE DECISION AFTER MUCH TRIAL AND SOME ERROR WAS TO USE NEUROLEPTANALGESIA AS AN ADJUNCT TO THE NERVE BLOCK TECHNIQUE, BECAUSE IT ENABLES THE PATIENT TO COOPERATE TO THE REQUIRED DEGREE.

I WILL LEAVE THE TECHNICAL DETAILS TO PROFESSOR MORICCA AND ASSUME THAT MANY OF YOU ARE FAMILIAR WITH IT. MY MAIN PURPOSE IN DISCUSSING IT TO THIS DEGREE OF DETAIL IS TO INDICATE THAT IT OFFERS A PRACTICAL AND IMPORTANT METHOD OF CONTROLLING PAIN DUE TO CANCER AND TO THE CONTROL OF THE CANCER ITSELF. SOME OF THE THRUST OF MY DISCUSSION WILL BE DIRECTED TOWARD THE IDEA THAT SOME CONCEPTUAL ASPECTS IMPORTANT TO THE PAIN PROBLEM CAN BE DEVELOPED BY A CRITICAL ANALYSIS OF THE

DATA..

IT IS VERY IMPORTANT IN CONSIDERING ANY EXPERIENCE IN AN IMPORTANT CLINICAL PROBLEM, TO BE CERTAIN THAT THE CLINICAL EXPERIENCES ARE UNDERSTOOD AND ARE REASONABLY ACCEPTED BY COMPETENT PEOPLE IN THE SAME FIELD. IT IS CRUCIALLY IMPORTANT, OF COURSE, TO UNDERSTAND THE MECHANISMS OF WHAT HAPPENS. IN THIS CASE THE MECHANISM OF PAIN RELIEF AND THE CONTROL OF NEOPLASTIC GROWTH, EVEN IF THE MECHANISM IS NOT UNDERSTOOD, BUT IF THE CLINICAL RESULTS ARE EXCELLENT, IT BECOMES THE OBLIGATION OF THE PEOPLE INVOLVED IN DEALING WITH PATIENTS WITH THESE PROBLEMS, TO TAKE ADVANTAGE PRAGMATICALLY OF WHAT IS KNOWN TO BE USEFUL, AND NOT TO BE INHIBITED BY A FAILURE TO UNDERSTAND THE MECHANISMS COMPLETELY.

MORICCA REPORTED IN 1974 THAT AT THE BEGINNING OF 1973, HE AND HIS COLLEAGUES HAD TREATED 687 PATIENTS WITH ADVANCED MALIGNANCY, AVERAGING A LITTLE OVER TWO PITUITARY DESTRUCTIVE BLOCKS PER PATIENT. (1) THESE PATIENTS NEARLY ALL HAD VISCERAL AND BONE METASTASES, MANY OF THEM WERE IN POOR CONDITION AND ALL OF THEM SUFFERED SEVERE PAIN DUE TO CANCER. IN THIS SERIES THE STARTLING FINDING TO MANY OF US FOLLOWING THIS LITERATURE IS THAT ONLY ONE PATIENT SHOWED NO BENEFIT AT ALL. TWELVE PATIENTS WERE IMPROVED WITHOUT COMPLETE PAIN RELIEF. SIXTY-NINE PATIENTS REQUIRED AT LEAST TWO INJECTIONS FOR PAIN RELIEF. THE INTERESTING AND TO BE EMPHASIZED FINDING, WAS THAT IN

605 PATIENTS "PAIN RELIEF WAS COMPLETE, IMMEDIATE, AND LONG-LASTING."

THESE RESULTS ARE SO GOOD THAT IT BEHOOVES ALL PEOPLE INVOLVED IN UNDERSTANDING THE THERAPY OF PAIN AND THE CONTROL OF CANCER TO BE AWARE OF THIS IMPORTANT FINDING,

MORICCA ALSO SPEAKS OF THE RESULTS THAT ARE NOT NECESSARILY FAVORABLE TO THIS METHOD OF THIS PAIN RELIEF PROBLEM BY DESTRUCTION OF THE PITUITARY WITH ABSOLUTE ALCOHOL. THE MOST IMPORTANT OF THESE ARE DIABETES INSIPIDUS, DIMINISHED ADRENAL AND THYROID FUNCTIONS AND THE REDUCTION OF LIBIDO. THE TECHNIQUE ITSELF, OF COURSE, HAS OTHER TRUE COMPLICATIONS AND THESE ARE VIEWED BY MORICCA AND HIS COLLEAGUES AS BEING TRANSIENT AND NOT VERY SIGNIFICANT.

IN THEIR HANDS CHEMICAL HYPOPHYSECTOMY WAS ENORMOUSLY EFFECTIVE. IT GREATLY EXCEEDED THEIR EVERY EXPECTATION AND IT DEALT WITH THE PAIN DUE TO CANCER CAUSED BY HORMONE DEPENDENT AS WELL AS NON-HORMONAL DEPENDENT TUMORS. THE PAIN, HE BELIEVES, IS REDUCED OR CURED INDEPENDENTLY OF WHAT HAPPENS TO THE NEOPLASTIC DISEASE.

IN THAT ARTICLE IN 1974, MORICCA DISCUSSED THE POSSIBLE MECHANISMS OF PAIN RELIEF. ONE OF THE POSSIBLE MECHANISMS OBVIOUSLY IS THE REGRESSION OF THE TUMOR ITSELF. THIS DOES OCCUR IN HORMONAL DEPENDENT MALIGNANCIES AND MAY BE

ONE OF THE MECHANISMS. HE PRESENTS A THESIS THAT A HORMONAL EFFECT ON PAIN IS ALSO A POSSIBILITY. THE EVIDENCE AS I EXAMINED IT SEEMS NOT TO BE VERY PERSUASIVE IN THIS REGARD. ANOTHER POSSIBLE EXPLANATION, AS MORICCA PROPOSES IT, IS THE POSSIBILITY THAT ABSOLUTE ALCOHOL EXERTS ITS ACTION BY SPREADING TO AREAS IN THE HYPOTHALAMUS. IF THERE IS DAMAGE TO THE CONNECTIONS BETWEEN THE HYPOTHALAMUS AND THE PITUITARY, THIS IS A POSSIBLE EXPLANATION FOR THE PRODUCTION OF ANALGESIA.

IN 1976 MORICCA UPDATED HIS RESULTS AND DESCRIBED AN EXPERIENCE OF SOME TWELVE YEARS IN WHICH DESTRUCTION OF THE PITUITARY WAS PERFORMED ON 1,026 PATIENTS. (2) THE RESULTS WERE SPECTACULARLY GOOD IN THAT FOR 885 OF THESE PATIENTS PAIN RELIEF WAS COMPLETE, IMMEDIATE, AND LONG-LASTING. ONE HUNDRED TWENTY-FIVE PATIENTS REQUIRED THREE BLOCKS TO ACHIEVE PAIN RELIEF. FIFTEEN PATIENTS RECEIVED ONLY PARTIAL RELIEF AND ONE PATIENT RECEIVED NO BENEFIT AT ALL. OF GREAT INTEREST ALSO WAS THE FACT THAT 30 PER CENT OF THE ADVANCED HORMONE DEPENDENT TUMORS, ON THE BASIS OF OBJECTIVE DATA, SHOWED IMPROVEMENT OR AT LEAST AN ARREST OF THE NEOPLASTIC DISEASE.

IN THIS PAPER MORICCA REVIEWS THE POSSIBLE MECHANISMS THAT HE SPECULATED UPON IN EARLIER PUBLICATIONS. ONE IS THAT THE PITUITARY IS LOCATED IN A CONFINED SPACE AND THAT INJECTION CAN CAUSE CELLULAR DESTRUCTION BY COMPRESSION. A SECOND CONCEPT IS

THAT THERE IS DIRECT CHEMICAL ACTION ON THE CELLS WITH SUBSEQUENT DEHYDRATION. AND THIRD, THE VESSELS ARE THROMBOSED WHICH RESULTS IN CELLULAR DAMAGE. IN THIS PAPER, THE THOUGHT THAT ALCOHOL MAY DIFFUSE AND INVOLVE THE PATHWAYS OF THE PITUITARY, THE HYPOTHALAMUS AND THE THALAMUS, COULD EXPLAIN THE ANALGESIC EFFECTS EVEN IN THE ABSENCE OF HORMONAL-BEARING TUMORS.

MILES AND LIPTON ALSO IN 1976, CONFIRMED THE ESTABLISHED FACT THAT ANALGESIA CAN BE PRODUCED BY PITUITARY ABLATION WITH HORMONAL DEPENDENT TUMORS. (3) THEY ACKNOWLEDGE MORICCA'S CONTRIBUTION TO THIS FIELD. THEY WERE UNABLE TO REPRODUCE MORICCA'S OUTSTANDING RESULTS BUT DID INDICATE THAT ONE-THIRD OF THEIR PATIENTS OBTAINED EXCELLENT PAIN RELIEF AND ONE-THIRD OBTAINED SOME RELIEF. THEY SUGGEST THAT THEIR LESS EFFECTIVE RESULTS THAN MORICCA'S MAY BE THE RESULT OF A DIFFERENCE IN TECHNIQUE SINCE THE BRITISH INVESTIGATORS WERE, AS THEY DESCRIBE IT, LESS AGGRESSIVE AND THEY SUGGEST THAT THEIR DIFFERENCE IN PROCEDURE MAY ACCOUNT FOR LESS SATISFACTORY RESULTS. THEY REPORTED A STUDY IN WHICH THEY ATTEMPTED TO ESTABLISH WHERE THE INJECTED MATERIAL WENT AFTER THE PITUITARY FOSSA HAD BEEN INJECTED. IN 20 PERCENT OF THEIR PATIENTS UPON USING A CONTRAST MEDIUM JUST BEFORE THE INJECTION OF ALCOHOL, THEY FOUND THAT

THE CONTRAST MATERIAL PASSED UP FROM THE PITUITARY FOSSA ALONG THE PITUITARY STALK, ALONG THE FLOOR OF THE THIRD VENTRICLE AND IN SOME INSTANCES EVEN BREAKING THROUGH INTO THE THIRD VENTRICULAR CAVITY. THESE FINDINGS SUGGESTED TO THEM THE POSSIBILITY THAT THE PAIN RELIEF MAY BE CAUSED BY DIRECT HYPOTHALAMIC INJURY. THEY CITE THE STUDIES OF SANO WHO OBTAINED GOOD RELIEF FROM PAIN IN 50 PERCENT OF HIS PATIENTS BY DESTROYING THE POSTERIOR HYPOTHALAMUS THROUGH AN APPROACH FROM ABOVE. THEY, THEREFORE, UNDERTOOK A STUDY IN CADAVERS TO DETERMINE WHERE A COLORED DYE WOULD BE FOUND WHEN THE TRANSPHENOIDAL INJECTION OF THE PITUITARY WAS PERFORMED. CRANIOTOMY WAS PERFORMED AFTER THE BLOCK, AND THE AREAS OF INTEREST WERE EXAMINED BOTH MACROSCOPICALLY AND MICROSCOPICALLY.

IN ALL CASES THE CONTRAST MATERIAL WAS AS EXPECTED IN THE PITUITARY GLAND. IN SOME INSTANCES, THE CONTRAST MATERIAL SPREAD INTO THE THIRD VENTRICLE. WHEN THE DYE WAS STUDIED CAREFULLY, DIFFUSE SPREAD WAS QUITE COMMON. THE STALK CONTAINED DYE IN EVERY INSTANCE, IT WAS ALSO FOUND IN THE VESSELS. THEY SUGGESTED THAT THE SPREAD OF THE MATERIAL CAN OCCUR THROUGH THE BLOOD VESSELS BUT IT ALSO COULD RUPTURE THE WALLS OF THE BLOOD VESSELS, AND IT MIGHT OCCUR LOCALLY WITHIN THE GLAND OR AT SOME SMALL

DISTANCE, SUCH AS IN THE HYPOTHALAMUS. THEY SPECULATE THAT INJURY TO THE HYPOTHALAMUS EITHER DIRECTLY BY FIXATION WITH ALCOHOL OR INDIRECTLY BY THROMBOSIS AND INFARCTION COULD RESULT IN INTERFERENCE WITH PAIN PERCEPTION OR WITH THE SUFFERING OF PAIN. THIS MECHANISM IF IT OPERATES, IS DUE TO THE INTERRUPTION OF THE HYPOTHALAMIC-THALAMIC CONNECTIONS.

THE JAPANESE INVESTIGATORS, TAKEDA AND HIS ASSOCIATES, ALSO REPORTED ON MORICCA'S TECHNIQUE IN A SMALL NUMBER OF PATIENTS. (4) THERE WERE 30 PATIENTS REPORTED WITH 43 INJECTIONS. PAIN RELIEF WAS INSTANTANEOUS IN MOST INSTANCES, AND THERE WERE MINOR COMPLICATIONS. AS REPORTED BY OTHERS, DIABETES INSIPIDUS (MORE OF WHICH WILL BE DISCUSSED LATER) WAS A MAJOR CONSEQUENCE OF THE INJECTION. THE OBJECT OF STUDIES BY RADIOGRAPHIC AND CAT SCAN, SHOWED THAT THE DESTRUCTIVE MATERIAL REMAINED IN THE SELLA AND NEVER TRAVELED TO THE HYPOTHALAMUS.

THEY DID ENDOCRINE STUDIES AND FOUND A CLEAR ASSOCIATION OF ANALGESIA WITH THE SUPPRESSION OF ANTERIOR AND POSTERIOR PITUITARY FUNCTION. IN FACT THEY BELIEVED THAT THEIR DATA SHOW THAT WITHOUT SUFFICIENT INACTIVATION OF BOTH THESE FUNCTIONS, PAIN RELIEF WOULD BE TEMPORARY OR INCOMPLETE. THEY OBSERVED THAT ACTH AND ALPHA-

ENDORPHIN IN THE CEREBROSPINAL FLUID WERE SIGNIFICANTLY ELEVATED IMMEDIATELY AFTER TREATMENT. THE CHANGE IN THESE PEPTIDES MAY PROVIDE A CLUE TO ELUCIDATE THE MECHANISM OF IMMEDIATE RELIEF FROM THE CANCER PAIN MEDIATED THROUGH THE CENTRAL NERVOUS SYSTEM.

IT SEEMS CLEAR TO THIS OBSERVER THAT THE REPORTS AVAILABLE, SUGGEST VARYING DEGREES - BUT ALL OF THEM VERY IMPRESSIVE - OF POSITIVE PRODUCTION OF ANALGESIA BY PITUITARY ABLATION WITH THE TECHNIQUE OF MORICCA. OBVIOUSLY OTHER INVESTIGATORS SHOULD PARTICIPATE IN THE STUDIES SINCE THEY ARE SO WELL ESTABLISHED NOW AND HAVE BEEN CORROBORATED ALTHOUGH THERE IS DIFFERENCE OF OPINION AS TO THE RELATIVE EFFICACY.

THIS CONCEPT AND STATEMENT THAT PAIN RELIEF CAN BE PRODUCED BY DESTRUCTION OF THE PITUITARY IS THE MOST IMPORTANT COMMENT TO MAKE IN THIS PRESENTATION. THE IMPORTANT AND INTERESTING SPECULATION AS TO THE MECHANISM BY WHICH IT OCCURS WHILE VERY IMPORTANT FOR FUTURE IMPROVEMENT IN PAIN CONTROL, IS SOMEWHAT LESS URGENT THAN IS THE FACT ITSELF OF BENEFIT TO PATIENTS WITH PAIN. THE FACT ALSO THAT SOME 30 PER CENT OF PATIENTS WITH HORMONAL DEPENDENT TUMORS CAN SHOW AN ARREST OR IMPROVEMENT OF THEIR DISEASE IS VASTLY SIGNIFICANT.

SOME SPECULATIONS HAVE ALREADY BEEN PRESENTED AS TO THE POSSIBLE MECHANISMS OF PAIN RELIEF BY PITUITARY ABLATION. THESE CONCEPTS DESERVE BOTH COMMENT AND CRITICAL ANALYSIS WITHIN THE LIMITS OF OUR VERY FRAGMENTARY INFORMATION AT THE PRESENT TIME.

FIRST A WORD ABOUT HOW FAR DESTRUCTION OCCURS AFTER BLOCK. THERE ARE CLEAR DATA ON BOTH ANIMALS AND MAN THAT ABSOLUTE ETHANOL DOES NOT DIFFUSE AND IN FACT DESTROYS WITHIN A VERY SHORT RADIUS WHERE IT IS INJECTED. THE FACT THAT ACCOMPANYING DYES MAY DIFFUSE HAS IN MY OPINION LITTLE TO DO WITH THE IDEA THAT ETHANOL WILL NOT DIFFUSE. THE ONLY POSSIBILITY OF DAMAGE TO HIGHER CENTERS BY ETHANOL IS NOT BY DIFFUSION BUT BY THE SUGGESTION MADE BY BOTH MORRICA AND LIPTON THAT THROMBOSIS OF THE CENTRAL VESSELS GOING TO THESE AREAS COULD CAUSE DAMAGE. A BETTER ANATOMIST THAN I WOULD HAVE TO COMMENT ON THE REASONABILITY OF THIS IDEA. THE SECOND POINT TO MAKE IS THE POSSIBILITY THAT EITHER AS A CONSEQUENCE OF BLOCKADE OR SOME AS YET UNKNOWN FACTOR MAY CAUSE CHANGE IN THE LIBERATION OF OTHER SUBSTANCES INCLUDING HORMONES AND ENDORPHINS WHICH COULD HAVE A BEARING ON PRODUCING PAIN RELIEF.

FOR INSTANCE, IT IS FAIRLY WELL KNOWN BUT HAS NOT BEEN MEASURED AND STUDIED PRECISELY THAT CERTAIN TYPES OF PAIN

ARE ASSOCIATED WITH A MARK OLIGURIA DURING THE DEVELOPMENT OF THE PAIN SYNDROME AND A MARK POLYURIA AS THE PAIN RECEDES. THIS SEQUENCE OF EVENTS IS FAIRLY COMMON IN MIGRAINE, AN IMPORTANT CAUSE OF HEADACHE BUT OBVIOUSLY A NON-MALIGNANT DISEASE. IT IS FASCINATING AND INTERESTING TO SPECULATE ON THE POSSIBILITY THAT SOMETHING RELATED TO POSTERIOR PITUITARY GLAND FUNCTION MAY HAVE A BEARING ON THE PRODUCTION OF PAIN RELIEF. IT IS MY SUGGESTION THAT SERIOUS AND SYSTEMATIC STUDIES OF THE RELATIONSHIP BETWEEN POSTERIOR PITUITARY FUNCTION AND ANALGESIA BE UNDERTAKEN. IT SEEMS AT LEAST IN THE HANDS OF THE PEOPLE STUDYING THE MIGRAINE PROBLEM AND IN THIS PARTICULAR ASPECT, TAKADA AND HIS ASSOCIATES MAKE THE POINT THAT WITHOUT POSTERIOR PITUITARY DYSFUNCTION THERE APPEARS TO BE NO ANALGESIA IN PATIENTS WITH CANCER.

ANOTHER FASCINATING AND CHALLENGING CONCEPT TO SPECULATE UPON IS THE POSSIBLE ROLE OF THE ENDORPHINS THEMSELVES. IN THE ONE STUDY AVAILABLE, ENDORPHINS ARE INCREASED IN THE CEREBRAL SPINAL FLUID WHEN DESTRUCTION OF THE PITUITARY IS PERFORMED WITH MORICCA'S METHOD. ITS POSSIBLE ROLE IN PRODUCING ANALGESIA IS UNKNOWN BUT CERTAINLY INTERESTING TO SPECULATE UPON. AN EVEN MORE EXCITING NOTION IN SOME RESPECTS IS THE FACT THAT THERE IS A BETA LIPO-PROTEIN IN THE PITUITARY FIRST DISCOVERED BY C. H. LI, WHICH HAS A FANTASTICALLY

INTERESTING CHEMICAL CONSTRUCTION. THIS BETA LIPO-PROTEIN SO FAR AS IS KNOWN, FUNCTIONS IN THE BUILDUP AND BREAKDOWN OF FATS IN THE BODY. IT HAS A CHAIN OF 91 AMINO ACIDS AND MOST INTERESTING IS THAT WITHIN THIS MOLECULE ITSELF THERE IS A COMPLETE SEQUENCE OF ENDORPHINS APPEARING WITHIN THE LARGER MOLECULE.

THE QUESTION THAT ARISES IS THAT WITH DESTRUCTION OF THE PITUITARY, IT IS ALMOST CERTAIN, EVEN THOUGH THERE ARE NO STUDIES THAT ATTEST TO THIS, THAT BETA LIPO-PROTEIN IS ALSO DESTROYED AND WITH ITS DESTRUCTION IS THE COMPLETE SEQUENCE OF ENDORPHINS. HOW DOES THE DESTRUCTION OF A BETA LIPO-PROTEIN CONTAINING A COMPLETE SEQUENCE OF ENDORPHINS RELATE TO THE PRODUCTION OF ANALGESIA? COULD IT BE THAT THE INTACT NATURE OF THE ENDORPHIN STRUCTURE WITHIN BETA LIPO-PROTEIN IS AN ANALGESIC ARRANGEMENT OF AN AS YET UNKNOWN SORT? COULD IT BE THAT ITS DESTRUCTION PERMITS OTHER MECHANISMS SUCH AS THE ONE DESCRIBED BY TAKEDA TO OPERATE? THERE ARE NO ANSWERS TO THESE INTRIGUING QUESTIONS AS YET, BUT THEY NEED AND WILL HAVE SERIOUS STUDY.

IN SUMMARY, THIS DISCUSSION HAS CENTERED EXCLUSIVELY ON THE MOST IMPORTANT PRAGMATIC AND EMPIRICALLY SOUND OBSERVATIONS FIRST MADE BY MORICCA AND CONFIRMED IN DIFFERENT DEGREES BY OTHERS THAT THE CHEMICAL ABLATION OF THE PITUITARY GLAND PRODUCES A SIGNIFICANT ANALGESIA IN

PATIENTS WITH CANCER PAIN AND A RETARDATION OR AN ARREST OF DISEASE IN HORMONAL-DEPENDENT CANCERS. THERE IS NO KNOWN MECHANISM FOR THE REDUCTION OR ELIMINATION OF PAIN WITH ABSOLUTE CERTAINTY. SPECULATION REVOLVES AROUND THE FACT THAT DAMAGE MAY OCCUR TO CONNECTING FIBERS BETWEEN THE HYPOTHALAMUS AND THE THALAMUS OR THAT THERE MAY BE A RELATIONSHIP BETWEEN POSTERIOR PITUITARY INSUFFICIENCY AND/OR FINALLY A RELATIONSHIP BETWEEN THE DESTRUCTION OF THE LIPO-PROTEIN IN THE PITUITARY GLAND WITH AN ENDORPHIN-BEARING SEQUENCE.

THE FACT THAT THE PRECISE MECHANISM OF ANALGESIA WITH THIS POWERFUL TOOL IS UNKNOWN, SHOULD NOT BE A DETERRANT TO CLINICIANS IN USING IT.

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