Glaxo Laboratories—

British marketing of Emmenin

November 17, 1933.

Dr. J.B. Collip,
Biological Building.

Dear Dr. Collip,

Enclsing is a copy of a letter received from Ayerst, McKenna and Harrison addressed to Sir Arthur on October 30th, 1933.

Yours faithfully,

Principal's Secretary

Encl.

3 8888

Ayerst, McKenna & Harrison
Limited

Ayerst PRODUCTS

Pharmaceutical Chemists

781 WILLIAM STREET,
MONTREAL, CANADA.

October 30, 1933.

Sir Arthur Currie,
McGill University,
Montreal.

Dear Sir Arthur,-

We wish to thank you for your letter of the 28th instant relative to registration of the word EMMENIN in Great Britain.

We very greatly appreciate your action in placing this matter in our hands, and can assure you of our best endeavour to conclude arrangements with Glaxo Laboratories, which will ensure control by ourselves of the integrity of the product which they may market under the name EMMENIN in Great Britain.

Very sincerely yours,

AYERST, McKENNA & HARRISON, LIMITED.

W. Harrison

WH/CB

Mr. Glassco ✓
Dr. Collip.

Please note & return to Principal

October
Twenty-eighth
1933.

Messrs. Ayerst, McKenna and Harrison, Limited,
781 William Street,
Montreal.

Dear Sirs:

Dr. Collip has forwarded to me a copy of the letter you addressed to him under date of October 17th.

The University has no objections to Glaxo Laboratories applying for registration of the word "EMMENIN" in Great Britain, provided that this name would be given only to placental extracts prepared in a manner that would provide adequate control by you of the integrity of the product and of such biological standards as would satisfy our Department of Biochemistry.

Yours faithfully,

Principal

Inter-department Correspondence

McGILL UNIVERSITY

October 24th, 1933.

Sir Arthur Currie,
Principal.

Dear Sir Arthur:

I am enclosing herewith copy of a letter addressed to me from Messrs. Ayerst, McKenna and Harrison. I would respectfully suggest that it be answered along the following lines:

In view of the fact that the Glaxo Laboratories are in reality the British agents for the firm of Ayerst, McKenna and Harrison, whom we have licensed to manufacture Emmenin, we should offer no objection to the filing of an application for registration of the word "Emmenin" in Great Britain by the former firm. It is not necessary that we give our permission, but rather that we state to Ayerst, McKenna and Harrison that we do not object to such procedure.

Yours sincerely,

J.B.Collip.

J.B.Collip

To Mr. Glassco:

JBC.M.
Encl.

Please prepare letter for me to sign and send Collip copy.

AWC:DM

AYERST, MC KENNA & HARRISON
LIMITED

781 William Street, Montreal.

October 17th, 1933.

Dr. J.B.Collip,
Dept. of Biochemistry,
McGill University,
Montreal.

Dear Doctor Collip:

A satisfactory basis for marketing Emmenin in Great Britain has not as yet been reached by Glaxo Laboratories, due to difficulty in obtaining registration of a suitable trade name.

Several names have been suggested, as you are aware, because the necessity for their protection, by this means, has been emphasized, in view of contemplated expenditures contingent on presenting Emmenin to the medical profession in Great Britain.

Our last suggestion to them was the word Emmenogen, which they thought very suitable. Unfortunately, they have advised us that their application for registration has been refused, owing to some similar word at present on the register.

They point out to us, and we agree with their viewpoint, that it is highly desirable that Emmenin be known by the same name, preferably, in Great Britain to that under which the product is recognized in Canada and the United States.

Under these circumstances, we feel the interests of all concerned would be best served if Glaxo Laboratories were to apply for registration of the name Emmenin in Great Britain, following the same procedure as we have in Canada and the United States.

We would point out further that the same reason would apply in permitting them to do so, as has applied in the case of ourselves, so far as the University is concerned - namely, the adequate control of the integrity of the product, and to ensure that it conform fully with your requirements for standardization. We have ascertained the Glaxo Laboratories would be prepared to give any undertaking in this regard which would be satisfactory to you or the University authorities. As for instance, they would agree to use the name solely with reference to placental extracts prepared in a manner described by yourself from time to time, and of such biological standards as would be subject, at all times, to your approval .

It was arranged during Mr. Jephcott's visit here last spring that we would manufacture in concentrate form all the material for their use on the British market, and thus ensure a direct measure of control. In this connection, we sent Dr. Cook from our laboratory to England this past summer, in order to assist them in arranging for proper check assays on concentrates of this nature which they are preparing to take from us.

You will recall that Mr. Jephcott quite definitely intimated their wish to preserve a close contact with your department and considered such could be best accomplished by obtaining their supplies directly from our laboratory.

If the University does not wish to correspond directly with Glaxo Laboratories regarding registration of the name Emmenin, we could suggest to them that they apply for it, but would want to be assured, in doing so, we were acting with the approval of the McGill authorities.

As a matter of fact, while the name is used in the scientific literature and an application for registration in Great Britain might not succeed, Glaxo Laboratories or any one else can make application at present, with rather good chances of success, and while they would not do so without your approval or ours, there is a reasonable probability that some other interests may do so.

It is apparently entirely unsound, according to British law, that we register the name in Great Britain and license its use to Glaxo, as was originally suggested.

Yours very truly,

Ayerst, McKenna and Harrison, Limited,

Signed - W.Harrison.

October 27th, 1933.

Dr. J. B. Collip,
Department of Biochemistry,
McGill University.

Dear Dr. Collip,

I have your letter of the 24th October and am agreeable to your suggestions outlined therein for answering the letter from Messrs. Ayerst, McKenna and Harrison. I shall have a letter prepared and will send you a copy.

Ever yours faithfully,

Principal

Ayerst, McKenna & Harrison
Limited

Pharmaceutical Chemists

781 WILLIAM STREET,
MONTREAL, CANADA.

Ayerst PRODUCTS

W. A. S. AYERST
W. J. McKENNA
W. HARRISON
HUGH McPHERSON
W. H. WALLACE

A.P.G. Lasseo.
Please note and return

May 12, 1933.

Sir Arthur W. Currie,
Principal and Vice-Chancellor,
McGill University,
Montreal.

Dear Sir Arthur,-

Your letter of May 6th is at hand granting us permission to register the name EMMENIN in Great Britain. This we will proceed to do at once.

Just as soon as we have received registration of the name THYROTROPHIN for Canada, we will immediately make application for registration of the same name in the United States and Great Britain.

In regard to the latter name, it is, of course, necessary that we first have registration in Canada.

Following up your telephone conversation in regard to the responsibility of Glaxo Laboratories, we would say that we have absolute confidence in this firm and you can appreciate that in our endeavour to place Emmenin on the British market, we are naturally anxious to form a connection with a firm that we believe is in the best position to carry out the work successfully.

We have been dealing with the Glaxo Laboratories for the last three or four years, and our relations have been of the most satisfactory character, and it is with every assurance we are entering into our present arrangements with them

Ayerst, McKenna & Harrison
Limited

Pharmaceutical Chemists

781 WILLIAM STREET,
MONTREAL, CANADA.

Ayerst PRODUCTS

W. A. S. AYERST
W. J. McKENNA
W. HARRISON
HUGH McPHERSON
W. H. WALLACE

for the sale of Emmenin, A.P.L. and Pituitary Substances.

The writer wishes to take this opportunity of thanking you for your many kindnesses in granting interviews to us and your very kind consideration in these matters.

Yours very truly,

AYERST, McKENNA & HARRISON, LIMITED.

WASA/CB

May 6, 1933.

Ayerst, McKenna & Harrison,
781 William Street,
Montreal, Canada.

Dear Sirs,

In reply to your letter of May 1st, re the placing on the British and other markets of Emmenin, A.P.L. and Pituitary Substances being at present elaborated in the Department of Biochemistry at McGill University, you have our permission to register the name "Emmenin" in Great Britain . I believe the name you have chosen for the other substance is "Thyrotrophin", and we will permit you to register that name also in Great Britain.

I think that is all that is necessary for you at the present time, as I understand the early registration of these names is what you most desire. The other matters mentioned in your letter can wait for further consideration.

Ever yours faithfully,

CANADIAN PACIFIC RAILWAY COMPANY

OFFICE OF THE CHAIRMAN AND PRESIDENT

MONTREAL
May 6th, 1933.

Dear Sir Arthur,-

I enclose herewith Sir George McLaren Brown's cable respecting Glaxo Laboratories.

It is not as specific as I would have liked with regard to the commercial reputation of the firm.

Sincerely yours,

Sir Arthur Currie, G.C.M.G.,
Principal & Vice-Chancellor,
McGill University,
MONTREAL, Que.

CANADIAN PACIFIC TELEGRAPHS

T.D. 1

CANADIAN PACIFIC COMMUNICATIONS

DIRECT COMMUNICATION WITH

THE INTERNATIONAL SYSTEM - IMPERIAL AND INTERNATIONAL

POSTAL TELEGRAPH - MACKAY RADIO COMMUNICATIONS LIMITED -

COMMERCIAL CABLES - ALL AMERICA CABLES IMPERIAL CABLES - BRITISH PACIFIC CABLE

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104

This is a full-rate Telegram or Cablegram unless otherwise indicated by signal in the check or in the address.

DL	DAY LETTER
NL	NIGHT LETTER
NM	NIGHT TELEGRAM
LCO	DEFERRED
NLT	CABLE LETTER
WLT	WEEK END LETTER

W. D. NEIL, GENERAL MANAGER OF COMMUNICATIONS, MONTREAL.

CBA440 79 FST 50 COML 5 STANDARD TIME

LONDON VIA COMMERCIAL

1933 MAY 5 PM 9 39

NLT WENTWORTH

MONTREAL

GLAXO LABORATORIES LTD MANUFACTURERS GLAXO SUNSHINE GLAXO MALTIC FOODS AND NUMBER OTHER PHARMACEUTICAL PRODUCTS STOP PRODUCT ENJOYS VERY GOOD NAME AND LARGELY ADVERTISED STOP GLAXO LABORATORIES LTD OWNED BY JOSEPH NATHAN AND COMPANY WHICH IS ITSELF LIMITED COMPANY WITH ISSUED CAPITAL SEVEN THIRTYEIGHT THOUSAND POUNDS PREFERRED ORDINARY

CANADIAN PACIFIC TELEGRAPHS

T.D. 1

CANADIAN PACIFIC COMMUNICATIONS

DIRECT COMMUNICATION WITH

THE INTERNATIONAL SYSTEM - IMPERIAL AND INTERNATIONAL

POSTAL TELEGRAPH - MACKAY RADIO COMMUNICATIONS LIMITED -

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W. D. NEIL, GENERAL MANAGER OF COMMUNICATIONS, MONTREAL.

STANDARD TIME

SEC CBA440

NLT WENTWORTH MONTREAL 29

1933 MAY 5 PM 9 39

TEN SHILLINGS SHARES QUOTED IN LONDON STOCK EXCHANGE AT THREE SHILLINGS STOP ORDINARY CAPITAL ISSUED IS THIRTYONE THOUSAND POUNDS NO DIVIDEND PAID ON THIS SINCE MARCH NINETEEN THIRTYONE

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£ 738000 . 10Sh. Shares

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£ 31000

Ayerst, McKenna & Harrison
Limited

Pharmaceutical Chemists

781 WILLIAM STREET,
MONTREAL, CANADA.

W. A. S. AYERST
W. J. McKENNA
W. HARRISON
HUGH McPHERSON
W. H. WALLACE

May 1, 1933.

Sir Arthur Currie,
McGill University,
Montreal.

Dear Sir Arthur,-

We are desirous of placing on the British and other markets Emmenin, A.P.L. and Pituitary Substances being at present elaborated in the Department of Biochemistry.

The processes governing their preparation have not been patented and accordingly may be prepared without hindrance, or control, by any interested manufacturer on that market,- a situation which, we suggest, could result in depriving the British public of the full therapeutic benefit of these substances, and at the same time, reflect discredit on such clinical observations as have been, or may be made on preparations conforming accurately with Dr. Collip's technique.

In Canada and the United States, these possibilities have been obviated by a plan which enables the Department of Biochemistry to exercise adequate control over the standardization of preparations sold on these markets and would suggest similarly effective control can be retained on the British market by the adoption of a somewhat modified plan.

Toward this end, we would be willing to manufacture the material for the British market and supply it to a British pharmaceutical house, Glaxo Laboratories, London, in whose integrity we have the greatest confidence. They, in turn, would undertake the actual work of introducing the various products to individual members of the British medical profession with whom they are in direct and very favourable contact.

Ayerst, McKenna & Harrison
Limited

Ayerst PRODUCTS

Pharmaceutical Chemists

781 WILLIAM STREET,
MONTREAL, CANADA.

W. A. S. AYERST
W. J. McKENNA
W. HARRISON
HUGH McPHERSON
W. H. WALLACE

Such work, if effectively done, requires the expenditure of considerable time and money, in addition to their knowledge of and real contact with the medical profession there.

Sound business practice recognizes that a reasonable safeguard be provided them against exploitation of the market created by their effort on the part of other manufacturers, British or foreign, at some later date, without themselves contributing in any way to the work of preparing a market.

The fairness of affording some such protection is further necessitated in view of your expressed wish that neither McGill University nor Dr. Collip's name should appear on trade packages containing these products sold in Great Britain.

As no protection can be afforded through the medium of patent rights, the alternative suggestion is that suitable coined names be registered and used by both Ayerst, McKenna & Harrison, Limited and Glaxo Laboratories, under which the substances could be manufactured and standardized by ourselves in Montreal, suitable control being, thus, exercised by the Department of Biochemistry.

With clinical experience in Great Britain built around these controlled products and prescribed under their adopted names, we submit the best interest of the Department of Biochemistry would be adequately served.

The present situation technically permits of the above procedure being followed without any reference to the University whatever in the case of all these products, with the possible exception of Emmenin, in which instance the University owns the name. Here again, any British or foreign manufacturers can successfully introduce this particular substance in Great Britain under any other name he may

Ayerst, McKenna & Harrison
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Pharmaceutical Chemists

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W. H. WALLACE

select, because of the fact that the name Emmenin is not at present known there to the medical profession generally. In fact, even the name Emmenin could be used there, unless McGill University determined to defend it at law.

In other words, at the present time, it would be practically as easy to introduce the substance under one name as another. We, on the other hand, are definitely convinced of the advisability of using the name Emmenin in Great Britain, as well as in Canada and the United States, and toward this end, suggest that either McGill University register the name in Great Britain, or acquiesce in this procedure being followed by ourselves, we, in turn, permitting Glaxo Laboratories to use it there.

This alternative is suggested in view of recognized difficulties, which, it has been stated, would confront the University in undertaking registration themselves in Great Britain.

In this connection, we suggest for your consideration the thought that in Canada and the United States some plan might be evolved whereby the name Emmenin could be transferred to ourselves and, thus, dissociate McGill University from any tangible connection with its commercial side.

Mr. H. Jephcott, Managing Director of Glaxo Laboratories, will be leaving from New York toward the end of the present week, in view of which we would appreciate a reply, if possible, early enough to permit us to contact with Mr. Jephcott before he sails, should any further discussion be necessary.

Yours very truly,

AYERST, McKENNA & HARRISON, LIMITED.

W Harrison

WH/CB

COPY FOR SIR ARTHUR CURRIE.

GLAXO LABORATORIES
56 OSNABURGH STREET
LONDON, N.W.1.

TELEPHONE: MUSEUM 8040
(9 LINES)
TELEGRAMS: GLAXOTHA, LONDON
CODE: NEW STANDARD

JOSEPH NATHAN & CO. LTD.
REGISTERED OFFICES:
16, ST HELEN'S PLACE,
LONDON, E.C.3.

PHARMACEUTICAL & FOOD PRODUCTS

Montreal, May 1, 1933.

Ayerst, McKenna & Harrison, Ltd.,
781 William St.,
Montreal.

Dear Sirs,-

In Confirmation of our conversation it is our intention, in furtherance of our policy to market biological products of merit, to add to our existing lines placental extracts, glandular and other products of medicinal value.

In this regard and with respect to such products as you are, or may be, in a position to supply we desire to work solely and exclusively by arrangement with yourselves, and to use products of your manufacture receiving them in bulk for ourselves to pack in manner appropriate to the various markets in which we operate. We understand that the processes utilised in the manufacture of these products have been published and with that in mind, it is to be appreciated that the prices which will from time to time be charged us by your-

selves must be such as will enable us to meet future competition of reputable houses.

Your products would be supplied on condition that we did not sell them in the North American markets.

We hold the view that it would be mutually advantageous that the products should be sold under the same names in all parts of the world and, if this policy commends itself to you, we should appreciate your indications that we shall be in order in registering such names wherever that course is necessary.

We understand that with respect to the word Emmenin, you will yourselves need to make enquiries. Will you please do so and inform us of the position with as little delay as possible since we wish promptly to take active steps to make the products available in the various markets?

For your information we attach a list of the markets in which we are working.

Yours faithfully,

GLAXO LABORATORIES

Director.

COPY FOR SIR ARTHUR CURRIE.

Great Britain & Ireland - London and Dublin

Australia - Melbourne & Sydney

New Zealand - Wellington, Hamilton, Aockland.

India - Subsidary Company, H. J. Foster & Company
Bombay, Calcutta & Madras.

Straits' Settlements.

Siam

Dutch East Indies.

China

Greece - Subsidary Company , Stan. Harvalias & Co.
Athens

Italy - Subsidary Company S.A. Nathan Bompiani
Verona

Turkey

Belgium

Argentina - Subsidary Company, C.C. Richardson S.A.
Buenos Aires.

Brazil

Chili

Cuba

In all of the above we have our own resident staff: in addition we work generally in all English speaking countries excluding North America and in most European countries.

Inter-department Correspondence

McGILL UNIVERSITY

February 4th, 1933.

Sir Arthur Currie,
Principal - McGill University,
Montreal.

Dear Sir Arthur,

I am enclosing a letter which is a bright spot in the gloomy world.

I enclose a copy of my answer, and assume that you probably wish to thank Mr. Ayerst in person. Apparently there are no strings to the gift, other than that it should be used in the Department of Biochemistry.

Faithfully yours,

C. J. Martin.

DEAN.

E/

February 4th,
1 9 3 3.

W. A. S. Ayerst, Esq.,
Messrs. Ayerst, McKenna & Harrison,
781, William Street,
Montreal.

Dear Mr. Ayerst,

I am in receipt of your very kind communication of February 3rd, announcing your intention of donating to McGill University, for the Department of Biochemistry, the sum of $5,000, to be distributed in divided amounts during the next three or four years.

I need not tell you how much we appreciate this gift, and the spirit in which it is given. It affords us a great encouragement in continuing the work, and especially to realize that we have such good friends as yourselves who enjoy our confidence.

I am forwarding your communication to Sir Arthur Currie, who, I am sure, will want to thank you in person for your generosity.

With all kind regards, believe me,

Very cordially yours,

C. F. H.

DEAN.

Ayerst, McKenna & Harrison
Limited

Pharmaceutical Chemists

781 WILLIAM STREET,
MONTREAL, CANADA.

Ayerst PRODUCTS

W. A. S. AYERST
W. J. McKENNA
W. HARRISON
HUGH McPHERSON
W. H. WALLACE

February 3, 1933.

Dean Charles F. Martin,
McGill University,
Montreal.

Dear Dean Martin,-

On many occasions we have approached various departments of McGill University, and in particular the Department of Biochemistry, for advice and assistance, which has always been courteously and generously extended.

When Dr. Collip announced his work on Emmenin, the University saw fit to entrust us with its preparation and general distribution, a gesture which we greatly appreciated as a tangible indication of confidence in us. We know that our connection with McGill University, particularly through the Department of Biochemistry, has been the means of creating a confidence in our firm that we would not have otherwise enjoyed.

As a modest evidence of our appreciation, it is our desire to make a contribution of $5,000.00 to McGill University for the particular use of the Department of Biochemistry. It is our intention to provide this fund in divided amounts during the next three or four years, or possibly in less time.

We especially request that this contribution be treated confidentially, any knowledge of it being confined to yourself, Principal Sir Arthur Currie and Dr. J.B. Collip, and the payments to be entered in the University records as donated by "Anonymous." We invite

Ayerst, McKenna & Harrison
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Pharmaceutical Chemists

781 WILLIAM STREET,
MONTREAL, CANADA.

Ayerst PRODUCTS

W. A. S. AYERST
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W. HARRISON
HUGH McPHERSON
W. H. WALLACE

your acquiescence for reasons which we have carefully considered.

In extending to McGill University our best wishes, we sincerely hope the future may enable us to be of some further service.

Yours very truly,

AYERST, McKENNA & HARRISON, LIMITED.

WASA/CB

January 30th,1933.

The Honourable Vincent Massey, P.C., LL.D.,
Batterwood House,
near Port Hope,
Ontario.

Let me thank you for your letter of the 26th in which you send me your cheque for $5,000 as the first of the two annual grants for research in our Department of Biochemistry which you have so generously offered.

May I say again how sincerely grateful I am to you for this encouragement of Dr.Collip's splendid work. I shall report the gift to the Board of Governors when they meet in a few days.

With all kind wishes,

I am,

Ever yours faithfully,

Principal.

Original filed with Deeds of Donation in College Vault.

Original filed with Deeds of Donation
in College Vault.

January 22, 1933.

The Honourable Vincent Massey, P.C., LL.D.,
Batterwood House,
near Port Hope, Ontario.

copy

Mr.Dear Mr.Massey,

I am indeed grateful for your letter of January 20th, confirming the proposal you made to me on the 12th instant to give two annual grants of $5,000. each for the purpose of assisting the researches in the Department of Biochemistry under Professor Collip's direction, on the subject of growth hormones in the anterior lobe of the pituitary body.

Dr.Collip is particularly delighted with this evidence of the interest his work has aroused. He is that sort of scientific investigator who has the faculty of achieving definite results. There is much scientific investigation which is undoubtedly interesting, but which deals only with the abstract. Such investigation is by no means to be condemned, nor must one always look for what may be called useful results; but I confess that, to me, there is an added pleasure when the new truth discovered can be made to serve in a positive way the well-being of mankind.

I shall place your letter before the Board of Governors at a meeting to be held soon, and I know that this evidence of your encouragement will be most gratefully received.

With kindest personal regards, I am,

Ever yours faithfully,

Principal.

Batterwood House,

near Port Hope, Ontario.

January 26, 1933

My Dear Sir Arthur,

Many thanks for your letter. I now have pleasure in enclosing a cheque from the Massey Foundation for $5,000 as the first of the two annual grants for research in your Department of Biochemistry.

With kindest regards,

Yours sincerely,

(Sgd) Vincent Massey

General Sir Arthur Currie, G.C.M.G., K.C.B.,
McGill University,
Montreal, Quebec.

Original filed with Deeds of Donation
in College Vaulty.

Batterwood House,
Near Port Hope, Ontario.

January 20,1933.

Dear Sir Arthur:

I am writing to confirm the proposal which I made to you last Thursday. As I said to you my wife and I have been much impressed by what we have heard of the importance of the work carried on by Dr.Collip of the Department of Biochemistry in the McGill Faculty of Medicine and also by what we have ourselves seen in Dr.Collip's laboratories. As a result I am very happy to be able to offer you on behalf of the Massey Foundation two annual grants of $5000. each for the purpose of assisting researches in this Department under Dr.Collip's direction on the subject of growth hormones in the anterior lobe of the pituitary body.

I shall be glad to hear from you at your convenience as to whether this proposal is acceptable.

Yours sincerely,

(Sgd) Vincent Massey,

Sir Arthur Currie, G.C.M.G., K.C.B.,
McGill University,
Montreal, Quebec.

Original filed with Deeds of Donation in College Vault.

See also letters from Dean Martin to the Principal, written from Edinburgh in 1930, regarding opinion of the Edinburgh authorities.

Claridge's
Brook Street W.1

16.5.30

Dear Sir Arthur

Just a wee line after an interesting chat with Lord Dawson re Collip's product. He suggests a committee in Montreal (say 3 or 4) to cooperate with an ad hoc group here representing not only M.R. Council - but also Edinburgh Univ. The Coll. of Surgeons - Coll. of Physicians & the Profession - as being a more catholic group than one body alone - It seems a good gesture & the English committee can be quite independent as to action.

Am off to Cambridge in a day or two - on the hunt

forfeit ideas those friends.
Very sad about Miller. So many friends
have gone west since Sept. home.
all kind regards. Chipman sails
Tomorrow.

Faithfully yours (in haste)

C D Marlin.

CANADIAN PACIFIC RAILWAY COMPANY'S TELEGRAPH

FORM T. D. 1 X

TELEGRAM

CABLE CONNECTIONS TO ALL PARTS OF THE WORLD

(Printed in Canada)

J. McMILLAN, General Manager of Telegraphs, Montreal.

STANDARD TIME

RAA113 60 COML LONDON 13

LCO GENERAL CURRIE MCGILL UNIVERSITY MONTREAL=

SAW CREWE WIESNER BOTH MOST FRIENDLY AND SYMPATHETIC ABOUT PATENT IN AMERICA ALSO SAW FLETCHER WHO MUCH PREFERS MCGILL ADHERE TO ORIGINAL IDEA OF ACCEPTING ROYALTY WITHOUT PATENT AND AFTER GIVING LILLY MONOPOLY AND TIME TO START IN AMERICA TO GIVE FORMULA THEN TO COUNCIL WITH FREE HAND WRITING NO HURRY ABOUT ACTION=

MARTIN=

Saturday, March 15, 1930.

Mr. Frosst called this morning to discuss with me the manufacture of Collip's preparation. I told him arrangements had been made with Ayerst McKenna and Company. He impressed upon me that the firm of Chas. E. Frosst & Company was bigger, better, did more research work and had a better standing, Ayerst, McKenna and Company being former employees of Frosst's. I told him that the contract had been made, and as far as this preparation was concerned nothing could be done. I suggested to him that he encourage the scientists in chemistry by providing scholarships for technicians and other assistance. In that way he would be helping the cause of science, helping these men in their work, securing their goodwill, helping a worthy cause, and probably helping the business of Chas. E. Frosst & Company. Something may come of it and I am to discuss the matter with Collip.

AWC:DM

Claridge's Hotel,

Brook Street,

London, W.1.

13th May, 1930.

My dear Sir Arthur,

I sent you from Edinburgh two days ago a hasty letter in which I described to you the attitude of Crewe and Weisner about the Collip discovery. In this letter I mentioned the fact that Weisner was anxious to have us under-take the work with a patent similar to that arranged in connection with the Insulin Fund, that Crewe was also in favour of University taking out patents, and that the attitude of their laboratory in general was both cordial and sympathetic, not only about the scientific and academic relations, but also with reference to the proposed plan of getting a royalty in one form or another from whatever commercial firms should undertake the work.

Since then I met Professor Clarke, who is Cushny's successor in the pharmacological department in Edinburgh. He mentioned to me for the first time the difficulties that had arisen in Great Britain over patents that had been issued, not only by Toronto, but also by Madison, Wisconsin, by Dick in Chicago, and by the Germans as well. He told me that the Medical Research Council of Great Brtiain were preparing to issue some statement with reference to their general policy, and that it would be as well for me to see Fletcher, the chairman of the Council.

On my return to London, I made an appointment, and before seeing him I received Simpson's timely cable, telling me of the progress of your arrangements and of your wish that I should see Fletcher in order to ascertain the attitude of the Medical Research Council with reference to patents on products discovered in University laboratories.

I had a most illuminating talk with Sir Walter Fletcher, in his office, and subsequently asked him and Dale to meet me here, in the hotel. I invited Chipman to be present, and between us we thrashed the whole matter out. As a result, I sent you the following cable to-day. (I withdrew my cable from Edinburgh before it went off, as I wanted to see Fletcher first.) The cable is as follows:-

"Saw Crewe and Weisner. Both most friendly and sympathetic about patent in America. Also saw Fletcher, who much prefers McGill adhere to original idea of accepting royalty without patent and after giving Lily monopoly and time to start in America to give formula then to Council with free hand. Writing. No hurry about action. (Signed) Martin."

I will now enlarge on the details of this cable. Both Fletcher and Dale deplored the issuance of patents by Universities as a bad principle for academic institutions, and as a very bad example for the future. They accepted the patent of insulin only because at that time there were no laws in Great Britain enabling them to standardise the products legally. Since then a law has been enacted here, in Great Britain, which makes it unnecessary for any University to protect themselves by patents in matters of this kind.

If McGill can dispense with the patents in Canada and the United States, and arrange with Lily in the United States and McKenna in Canada by contract to make and sell the product in those countries, only giving us a royalty on the proceeds, it would receive the approval of the Medical Research Council. Certainly it will be a relief to them to know that McGill will stand on a higher plane than if they were to arrange for the sale of the product through any patent. They are therefore agreeable to allowing Lily and McKenna to get a fair start of, say, three months, or whatever time is necessary in fairness to them, and we have suggested to them that Collip might send his formula to the Medical Research Council for their safe keeping and to be used for further research and sale by them at such time as Collip is willing to release it to Great Britain.

I understand that Collip has written to Sir Walter Fletcher, asking if Burroughs & Wellcome would be a suitable firm to entrust the formula to. This, of course, goes without

saying, but there was an implication that our University would desire to control the product and perhaps receive a royalty from the English firm if the manufacture were carried out in Great Britain. It seemed to both Chipman and myself, ~~both~~ wiser to have no commercial arrangements of any kind with any firm in Great Britain, though I think it might perhaps be understood that the sale of the British product in America should be restricted in some way, so as not to interfere for a reasonable length of time with the sale of any American or Canadian product that is made. It is, of course, understood that Lily will not try to sell his product in Great Britain.

I hope this very lengthy screed is not so involved as to obscure the main thought that is in our minds. Briefly, after hearing all the evidence, we doubt if it is wise for McGill to issue a patent, and we would certainly have a better academic standing among our British colleagues if we refrained. The original arrangement, without a patent, seems to be the better policy.

So long as Lily has a fair start with the manufacture and sale of the product, there would seem to be no hurry for details. When Collip arrives, he can discuss the matter further with all those concerned. I would just like to add that both Dale and Fletcher spoke of Collip's personal academic attitude in the very highest terms.

I will write you about other matters later.

With all kindest regards,

Faithfully yours,

C. J. Martin.

Sir Arthur Currie,
McGill University,
Montreal, CANADA.

February Twelfth,
1 9 3 0 .

Messrs. Ayerst, McKenna & Harrison, Ltd.,
Pharmaceutical Chemists,
M o n t r e a l .

Dear Sirs,

I acknowledge your letter of February tenth and thank you sincerely for your kindly congratulations.

We welcome the interest of a Canadian firm in the manufacture and sale of the product and have pleasure in replying to the various clauses of your letter as follows:-

Clause 1.	Acceptable.
Clause 2.	Acceptable.
Clause 3.	Acceptable.
Clause 4.	Acceptable.
Clause 5.	Acceptable.
Clause 6.	Acceptable
Clause 7.	Acceptable. - The name of the preparation is to be determined by ourselves.

Clause 8.	The intervals at which reports are to be made by you to be fixed in a definitive contract which will supersede these letters.
Clause 9.	Acceptable in principle, the meaning of "net sales" to be fixed in our definitive contract.
Clause 10.	The University will assign to you all such rights as it possesses and will undertake to grant no rights which will entitle other firms to bring the product into Canada or to manufacture or dispose of it here. As you will be the sole assignees of our rights in Canada, it will be your duty to protect yourselves against infringement. This we understand to be the intention of your clause 10.

We are prepared to assign to you on similar terms all our rights for the British Empire, exclusive of Great Britain and Ireland.

Our whole arrangement will be embodied in a formal contract which will supersede these letters.

Yours faithfully,

Principal.

February Eleventh,
1 9 3 0 .

Mr. George W. Taylor,
Commissioner of Excise,
O t t a w a .

Dear Sir,

A placental extract which constitutes a new therapeutic agent has recently been developed at this University.

It is proposed that the pharmaceutical house of Ayerst, McKenna & Harrison undertake the production of this extract on a commercial basis, but under our direction. It is essential that large quantities of a special denatured alcohol be used in the process. The formula 23-A, which is available in the United States but not in Canada, is the one recommended for use.

We would therefore ask you to issue a special permit to this firm which would allow them to import this special denatured alcohol.

Yours faithfully,

Principal.

McGILL UNIVERSITY
MONTREAL

DEPARTMENT OF BIOCHEMISTRY
BIOLOGICAL BUILDING

February 11, 1930.

Sir Arthur Currie, G.C.M.G.,
President, McGill University,
Montreal.

Dear Sir Arthur:-

I am enclosing herewith a letter which I have received from the firm of Ayerst, McKenna and Harrison.

I might explain to you that this special formula, 23A, referred to has of late years not been acceptable to the Canadian authorities and it would therefore be necessary for a special permit to be granted for its importation. I am given to understand that there will be no difficulty in regard to this if it is specifically stated what purpose it is for, and also pointed out that we are asking this for one firm only.

Trusting that you will be able to give this matter your attention,

Yours sincerely,

JBC/EEW

Handed letter for Mr.Taylor to Mr.Ayerst
Feb. 11th, 1930.

Ayerst, McKenna & Harrison
Limited

D.McMurray
Secretary to
Principal.

Ayerst PRODUCTS

Pharmaceutical Chemists

W.A.S.AYERST
W.J.McKENNA
W.HARRISON
HUGH McPHERSON
W.H.WALLACE

MONTREAL, CANADA

February 10, 1930.

Dr. J.B. Collip,
Department of Biochemistry,
McGill University,
Montreal.

Dear Dr. Collip:-

We have been in touch with the Department of Excise at Ottawa in regard to securing specially denatured alcohol for the economical manufacture of placental extract Collip.

We are advised that our request will receive favorable consideration provided we secure a letter from Sir Arthur Currie, Principal of McGill University, addressed to Mr. George W. Taylor, Commissioner of Excise at Ottawa advising him that Ayerst, McKenna & Harrison, Montreal, is authorized by McGill University to manufacture placental extract Collip, and that for the economical manufacture of the same, it is necessary to have denatured alcohol, the same formula as recommended by Dr. J.B. Collip, which formula is designated as 23 A (alcohol and acetone) U.S.A. formula.

We would, therefore, thank you to give this your early attention and secure said letter from Sir Arthur Currie, so that we may make arrangements at Ottawa at once and thereby save delay.

Yours very truly,

AYERST, McKENNA & HARRISON, LIMITED.

W.A.S. Ayerst Pres

WASA/CB

ELI LILLY AND COMPANY

INDIANAPOLIS, U. S. A.

OFFICE OF
J. K. LILLY, PRESIDENT

February 10, 1930.

Sir Arthur Currie, Principal,
McGill University,
Montreal, Quebec,
Canada.

Dear Sir Arthur:

Your very kind letter to our President, Mr. J. K. Lilly, is much appreciated and we are forwarding to you today a tentative agreement which we hope covers the main points desired by McGill University. A meeting with our patent attorneys will occur today and we shall push this along as quickly as possible. Unfortunately, caveats were cancelled in connection with patents by the United States Senate some years ago but we shall use every possible endeavor to protect our mutual interests.

I shall arrive in Montreal late Wednesday evening as Dr. Collip says you desire to see some of us on Thursday. I shall get in touch with Dr. Collip upon my arrival at Montreal.

Very sincerely yours,

Eli Lilly

Vice President.

EL-B

Air Mail

FAST DAY MESSAGE [X]
DAY LETTER [ ]
NIGHT MESSAGE [ ]
NIGHT-LETTER [ ]
L-768

CONFIRMATION OF TELEGRAM

SENT BY

ELI LILLY & CO.

CITY STATE VIA

DATE
TIME
BY
CHARGES

FEBRUARY 10 1930

DR J B COLLIP
DEPARTMENT OF BIOCHEMISTRY
MCGILL UNIVERSITY
MONTREAL QUEBEC CANADA

ARRIVING MONTREAL WEDNESDAY TEN TWENTY P M HOTEL MOUNT ROYAL STOP
PLEASE LEAVE MESSAGE THERE AS TO OUR PROGRAM THURSDAY STOP FORWARDING
AIR MAIL TODAY TENTATIVE CONTRACT TO PRINCIPAL CURRIE

ELI LILLY

EL-B
PAID(ED&Co)

ELI LILLY AND COMPANY

INDIANAPOLIS, U. S. A.

OFFICE OF
J. K. LILLY, PRESIDENT

February 1, 1930.

Sir Arthur Currie, Principal,
McGill University,
Montreal, Quebec, Canada.

Dear Sir Arthur:-

Dr. Collip has brought to us information concerning the development of an Ovarian Hormone that presents all the appearance of being a very important discovery. As the scientific staff of this Company is organized and possesses the proper personnel for cooperation in making such discoveries valuable to the medical profession, the privilege of cooperating with your institution in devising methods of manufacture, testing and presenting the hormone to the medical profession is respectfully invited.

Several items of this nature have been successfully developed in our laboratories and it seems quite certain that our cooperation would be of real service. A manufacturing process could no doubt be developed with reasonable promptness and McGill University supplied with the product without charge for such clinical investigation as might be necessary.

It would be our further suggestion, instigated by experience, that your institution could well confine this development work and its presentation to the medical profession to one institution. When a number of manufacturers are permitted to go on to the market with the same item under license, expensive competition results and the price must be made to cover this expensive rival advertising and exploitation. When placed in the hands of one corporation an immense amount of expense is avoided and the price can be made lower. Toronto limited the time of exclusive use but at the end of that period expensive competition began. Harvard University cooperated with this Corporation only in the development of Liver Extract. The Rockefeller Institute granted exclusive license for Tryparsamide to the Merck Company; Kendall gave exclusive to Squibb for Thyroxin. We believe this

latter plan is sound, and we submit the thought to you for your consideration.

Should you decide in favor of cooperating with this Company we are quite willing to bear all expense of development and if and when it is placed upon the market, to contribute to your institution for defraying expense of research an amount equal to 5% of net sales.

All of this, of course, should be contingent upon whether or not there are any patents found to interfere with the whole project.

Our organization is in a position to proceed at once with the development of this interesting substance, and some of us would be very glad to come to Montreal to discuss the matter with you and to make a final agreement, provided you desire to do so.

Sincerely yours,

Josiah K. Lilly

JKL.C

President.

February 5th, 1930.

Josiah K. Lilly, Esq.,
P r e s i d e n t ,
Messrs. Eli Lilly & Company,
Indianapolis.

Dear Mr. Lilly,

I acknowledge your letter of February 1st last, concerning the Placental Hormone developed by Dr. Collip, and I am glad to say that we shall welcome your co-operation in its manufacture.

We accept your suggestion that you should be the sole agents for the development of Dr. Collip's preparation and its presentation to the medical profession. We understand that this is for the United States only.

We are prepared to accept in principle the proposals that you should (a) bear the expense of development; (b) supply us with the product without charge, for such clinical investigation as may be necessary; and (c) pay us an amount equal to five per cent (5%) of the <u>net sales</u>,- which we understand to mean gross sales less returns and any discounts taken.

We also ask that you agree to assign to this University any patents on improvements or alterations to the process which you may develop.

It is understood that you are at once to apply on behalf of Dr. Collip and this University for a United States patent, and that you will file a caveat and take all necessary or advisable steps to protect our mutual interests. We also agree that if you are entirely prevented from manufacture and sale by other parties having prior rights, our contract will cease to be binding.

We should welcome a visit from representatives of your organisation, and would be willing at that time to enter into a more formal contract superseding these letters.

Ever yours faithfully,

Principal.

Introduction

THIS AGREEMENT, made at Montreal, Quebec, this _____ day of _____, 19 , by and between _____ of _____, hereinafter known as the "Licensor", and Eli Lilly and Company, a corporation organized under the laws of the State of Indiana, with its principal offices in Indianapolis, hereinafter known as the "Licensee", WITNESSETH:

Preamble

WHEREAS, the Licensor has discovered a certain new and useful substance and/or process for making same, described as a placental hormone or hormones which discoveries are still in the experimental stage, and

WHEREAS, said Licensor believes said inventions to be patentable and will promptly apply for patents thereon, in United States of America, and

Inventor's Purpose in Contract

WHEREAS, the Licensor now requires the assistance of a competent research laboratory to develop and perfect said discovery so as to make available for public use all possible commercial products thereof, of the best possible quality, at as early a date as possible, all of which assistance the Licensee is prepared to furnish, and

WHEREAS, the Licensor will thereupon require a competent manufacturing organization to produce and distribute said products in the purest possible form, in sufficient quantities to meet the public need and at a just and fair price, all of which the Licensee is likewise prepared to furnish, and

Company's Purpose

WHEREAS, the Licensee is ready, able and willing to furnish within reason its staff of scientists, laboratory, financial assistance and manufacturing and

sales organization to meet said requirements and also to compensate the Licensor by royalties, upon any of said products that it may desire to make and vend, all in return for the rights to accrue to it hereunder and as herein fixed.

The Grant

NOW, THEREFORE, in consideration of the mutual promises and undertakings of the parties as herein fixed,

IT IS HEREBY AGREED:

1. The Licensor hereby grants to the Licensee [the exclusive] right to make, use and sell any or all products that may come under the discovery above defined and under any improvement or addition thereto, as well as the exclusive right to use said process and any addition or improvement thereto, in the United States of American and its Dependencies. (We should appreciate an extension of non-exclusive licenses for as many foreign countries as possible. May we have your ideas upon this important subject?) The rights granted hereby shall be as broad as those now owned or hereafter acquired by the Licensor in the field covered hereby, subject, however, to the conditions and limitations hereinafter set out.

a license to exercise all its rights

Program of Investigation

2. Said Licensee will promptly produce and properly test a sufficient amount of said product to properly determine its clinical value, furnishing the same, without cost, to the Licensor and a reasonable number of clinicians to be selected by the Licensor.

3. The Licensee agrees to commence the commercial manufacture and sale of said product within six months after the clinical work has proven, in the mutual judgment of the parties hereto, the advisability of marketing said product.

4. If, on the other hand, the Licensee upon investigation, decides that any such substance and/or process is not new and valuable, or that the same cannot be sold and/or used profitably, then the Licensee shall return to said Licensor all such written or printed information peculiar to any such substance and/or process so rejected, which it may have received from said Licensor, without retaining possession of any copy thereof: whereupon all rights theretofore granted to the Licensee as to any such shall fully revert to the Licensor and the Licensee will thereupon reassign, upon demand, any and all rights to any such substance and/or process theretofore acquired by it.

Mutual Pledge of Help and Secrecy

5. The parties hereunto will, in good faith, mutually cooperate along the lines herein contemplated, to develop and perfect said method and/or product and to safeguard effectually their mutual interests. To that end neither party hereto will voluntarily disclose to any third party any facts or information, or furnish any materials to any such third party, except insofar as may be necessary in experimentation, testing, the development of the patents and the publishing of the necessary scientific papers.

6. If the Licensee should desire the Licensor or a representative of the Licensor to come to Indianapolis to give assistance or specific information in the making of any such substance or in the use of any such process, the Licensor will do so on request and at the expense of the Licensee for actual and necessary hotel and travelling expenses. Such visits to be made at the convenience of the Licensor and not to exceed more than two days per month.

Improvements

7. Should any change or improvement be made by either party in any product or process covered by this agreement, the same shall come within the operation and terms of this agreement as though specifically described herein. Any improvement made by the Licensee and considered worthy of patenting by mutual agreement of the parties hereto, shall be patented by and at the expense of the Licensee and assigned to the Licensor.

Patent Arrangements

8. The Licensee at its own expense will apply at once on behalf of Dr. Collip and the Licensor for a patent in the United States of America, and take all necessary and advisable steps to secure this patent and to protect the mutual interests of the parties hereto.

Litigation

9. In the event litigation becomes necessary or advisable for the prosecution or defense of any right under any patent covered hereby, the action of the parties with respect thereto shall be determined by their mutual consent and at their equal cost and expense, but the total necessary expense thereof shall be furnished from time to time by the Licensee, who shall, however, charge one half of its said disbursements to the royalty account of the Licensor and be relieved from the payment of royalties to that amount.

out.

licensee pays all expenses.

Royalty Payments

10. The Licensee will pay, during the term, in the manner and on the conditions herein provided, a royalty of Five percent (5%) to the Licensor, upon the regular net selling price to its wholesale distributors of such of said substances covered hereby as it may sell after deducting any returns from or allowances to the trade.

from gross sales

11. Payments of royalty shall be made quarterly as soon after the end of each calendar quarter as the Licensee is reasonably able to determine the proper amount thereof.

12. In the event any product developed hereunder by the Licensor, and submitted to the Licensee, is and remains protected by patent monopoly, then the obligation to pay royalty shall continue during the life of such monopoly and no longer, until the termination of the patent herein mentioned or any extension thereof. If no patent is obtainable but the Licensor continues to cooperate only with the Licensee in the United States of America, then the obligation to pay royalty shall continue for seventeen years (17) from the date of this agreement.

Right to Examine Records

13. The Licensee shall keep a full, true and exact account of the net quantity or quantities of said product sold, and the Licensor, or his authorized agents, shall have the right at all reasonable times to examine the accounts and records of the Licensee insofar as they relate to the sales of any substance subject to royalty described herein.

Control of Quality

14. All products sold or distributed by the Licensee under this license shall conform to reasonable standards of strength, stability, composition and purity from time to time established by the Licensor. The Licensor shall have the right from time to time or at all times to require the Licensee to submit to the Licensor or their designated representative or representatives, samples of each or any or every lot intended for sale or distribution by the Licensee before any of such lot is bottled or packed for sale or distribution by the Licensee, or is sold or distributed by the Licensee, and in every such case none of such lot shall be sold or distributed by the Licensee until it shall have met the standard of strength, stability, composition and purity established by the Licensor.

15. If the Licensee shall, in the sale or distribution of said product, fail to use safe, efficient and adequate methods, or shall sell or distribute any product which fails to comply with the standards of strength, stability, composition and purity from time to time fixed by the Licensor, the Licensor, by sixty (60) days prior written notice sent by registered mail, addressed to the Licensee, may suspend the license hereby granted, and all rights and privileges hereby conferred until the requirements of the Licensor as to methods and standards are complied with by the Licensee to the satisfaction of the Licensor.

16. If the Licensee, after receiving any such notice, shall for six months fail to meet the established standards of strength, stability, composition or purity of said product, the Licensor shall (notwithstanding any waiver by the Licensor or any failure by the Licensor to take advantage of any prior conditions, failures or defaults) have the right to terminate forthwith the license hereby granted.

Licensor's Control of Literature

17. No new product covered hereby or special literature describing the same shall be released by the Licensee without the consent and approval of the Licensor being first obtained, should he so desire and so instruct in writing. All advertisements in medical and pharmaceutical journals and in the general advertising of the Licensor shall be based only upon statements appearing in the special literature which has had the approval of the Licensor.

Control of Price

18. The Licensee shall, at all times, sell the product covered hereby at moderate, fair and reasonable prices, consistent with manufacturing and market conditions then existing. If the Licensor believes that the

selling prices of the Licensee are excessive or unfair, and the parties hereto cannot come to a satisfactory agreement, regarding a readjustment of same, the matter shall be submitted to a board of arbitration composed of three chartered accountants, one appointed by each of the parties hereto, and the third selected by the two so appointed, and the finding of the majority of such arbitrators shall be final and the Licensee shall have the right and privilege of electing whether they will fix the selling prices in accordance with such finding or terminate the license hereby granted. If the Licensee fails to make such election within sixty (60) days from the date of such finding, or to observe, abide by, and carry out the election when made, the Licensor may forthwith terminate the license hereby granted, and the Licensee shall have no claim, recourse or cause of action against the Licensor for so doing. Each of the parties hereto shall pay the expense of the arbitrator selected by it, and the expense of the third arbitrator shall be borne equally by the two parties.

Licensee's Right to Cancel

19. In the event the Licensee decides it cannot profitably place upon the market, or manufacture and sell any substance and/or use any process covered hereby, and if and when it discontinues the manufacture and sale of the same and/or use of said process, whatever rights it may have acquired in said substance and/or process, respectively, including trade names, etc., shall thereupon revert to the Licensor and become his property. At the same time all obligations of said Licensee in respect to the above mentioned item shall forever cease and determine, except as to any royalty obligation then unliquidated.

Official Signature of Licensee

20. This agreement shall become binding upon the Licensee only when it is signed by an officer thereof.

Testimonium 21. IN WITNESS WHEREOF, the parties hereto have executed this contract in duplicate, on the date first above mentioned.

WITNESS:

_____

_____ _____
Licensor

_____ ELI LILLY AND COMPANY

_____ By _____
Authorized Officer

Montreal Man First In Race, Says Scientist

Special Wireless by J. E. Poole, The Star's Resident Correspondent.

LONDON, Feb. 15 — Commenting on the discovery affecting the hormone by Dr. Collip of McGill University, Doctor B. P. Wiesner, a young Austrian scientist, who is a member of Professor Crew's group of physiologists at Edinburgh University, says:— "I am not surprised that Dr. Collip has been able to bring the work to this point as he is an able scientist. Professor Crew and I were engaged on this research work for two years. Last year at Boston I explained our discoveries to Dr. Collip and outlined the methods by which many men are working.

"Dr. Collip has been first in the race."

Professor Crew said in an interview with The Star:—"Medical thought has been advancing steadily toward this point. Dr. Wiesner reached it first and now Dr. Collip is reported to have made application of the discovery a practical possibility."

* * *

LONDON, Feb. 15, — (B.U.P.)— The gland secretion discovery of Dr. James B. Collip, chairman of the Department of Biochemistry at McGill University, Montreal, has excited much interest throughout Britain, particularly among medical men, who agree that if the claims made for the new drug can be substantiated, the discovery will be of the greatest value.

Eminent British gynaecologists such as Dr. Comyns Berkeley and Dr. Fairbairn, to whom Dr. Collip's discovery was reported by the British United Press, refuse, however, to make any comment until they are more familiar with the details declaring that it is impossible for them to express an opinion of any value at the present time.

One doctor, whose name cannot be disclosed, says that the full value of the discovery cannot be decided until the prepared hormone has been more fully tried on a human subject. "According to the accounts received," he said to the British United Press, "the new substance should be of great value in the treatment of certain defects to which women are subject."

* * *

DR. WEISNER, according to Professor Crew, is entitled to much credit in connection with Dr. Collip's success.

"I invited him (Dr. Weisner) to come to Edinburgh because I regard him as one of the most promising young men in Europe," said Professor Crew. "He has been engaged on this question for several years, and his discoveries are now proving of great value."

THREE ARE DEAD

McGill Medical Workers Make New Discovery

Doctors Collip and Campbell Isolate New Remedial Hormone

RESULTS REMARKABLE

Substance Will be Means of Curing Feminine Disorders

An extract which offers a remedial agent for certain feminine disorders has been derived in the McGill biochemical laboratories, it was announced yesterday by the Faculty of Medicine. This discovery, which is one of the most remarkable made at McGill, is the result of the work of Dr. J. B. Collip.

The discovered substance is of great importance, according to the authorities, affecting as it does almost every woman, and has opened up a wide field for clinical investigation.

The substance which Dr. Collip has succeeded in purifying and standardizing is a hormone having effects somewhat similar to those of the pituitary gland. The drug, states Dr. C. F. Martin, influences in a very remarkable manner the metabolism and general health of the patient receiving it.

Publish Results

Articles by Dr. Collip and Dr. A. D. Campbell, who carried out clinical observation in connection with this work, appear in the current number of the Canadian Medical Journal, which appeared on yesterday, and these give complete technical details of the discovery and of the laboratory experiments that have been conducted.

All of this work has been based upon earlier investigations carried out in other countries, more particularly the work of Weisner of Edinburgh, and which, until the present time, had not been brought to a successful conclusion.

Sir Arthur Comments

Sir Arthur Currie, commenting upon the discovery said:

"Everyone at McGill University rejoices exceedingly that complete success has rewarded the long and patient efforts of Professor Collip and his capable assistants in the biochemical laboratories of our medical school. For weeks we have known of the experiments and were cheered by reports from time to time that success was in sight."

Dr. Campbell, will take charge of further investigation and the application of the new hormone in both the Royal Victoria and the Montreal General Hospitals.

...iscovery at McGill ...imed as Great Boon

(Continued from Page 1)

...ressing menopausal symptoms and ... two cases of dysmenorrhoea." The report then proceeds to give details of several cases thus treated, and showing effective results.

NOT A PANACEA.

Dr. A. D. Campbell further warns, in discussing this discovery, that it is not to be regarded as a panacea for every disorder that can afflict women. "Our experience thus far" he says, "is that patients shoulud be selected, placed in hospitals, and thoroughly investigated before and during the administration of this extract. It is hoped that such studies will throw new light upon these problems, and that this study may help to unmask the atrology of certain so-called toxoemias."

Dr. Martin, Dean of the Medical School of McGill declares that this is a remarkable discovery, which should bring relief and comfort to countless thousands of women throughout the world. "Discoveries that add to the material wealth of people and nations are highly desirable, but one that gives health and joy and consequent happiness to men and women deserves our everlasting gratitude," he says.

PRINCIPAL PLEASED.

Sir Arthur Currie, principal of McGill, says of the discovery: "Everyone at McGill rejoices exceedingly that complete success has rewarded the long and patient efforts of Professor Collip and his capable assistants in the biochemical laboratories of our medical school. For weeks we have known of the experiments and were cheered by reports from time to time that success was in sight."

RESULTS GOOD

Dr. W. W. Chipman, emeritus professor of obstetrics and gynaecology of McGill University, expressed great interest in the subject. "The results already secured both in the laboratories and in the hospitals thoroughly justify a strong belief in the efficiency of this new drug. Professor Collip stands already among the foremost workers in the field of biochemistry, and this recent research can but greatly add to his distinguished reputation.

"As is well known, the biochemists both in Europe and in America have for some time, been engaged in the solution of this very problem. And we congratulate Professor Collip on his recent achievement.

"The clinical application of this new therapy is in the hands of Dr. A. D. Campbell both at the Montreal General and the Royal Victoria and Montreal Maternity hospitals. Cases deserving this treatment are to be segragated in these two hospitals under Dr. Campbell's supervision and care.

DR. COLLIP'S CAREER.

Dr. James Bertram Collip, while still under 40 years of age, has come to be recognized as one of the leading biochemists in America. He was appointed to the chair of biochemistry in McGill University, medical faculty, in the autumn of 1927.

Graduating from the University of Toronto in 1911 with special honors in physiology and biochemistry, Dr. Collip shortly afterwards proceeded to take a graduate course in these subjects and took his Ph.D. degree in 1914.

The first appointment of Dr. Collip was to a lectureship in the University of Alberta. Subsequently he received his doctorate of science at the western university and later was appointed to a professorship. He then received his M.D. and also gained the distinction of being elected to a fellowship in the Royal Society of Canada.

Dr. Collip first come into public notice when the discovery of insulin was made by Dr. Frederick G. Banting and Dr. Charles H. Best. He was associated with these two scientists at the time of this momentous discovery and shared with Dr. Banting and Professor McLeod in the sum of money received in connection with the Nobel prize award.

NOTABLE WORK.

The most notable work accomplished by Dr. Collip since 1922 has been in connection with parathyroid glands, the active principles which he has discovered and isolated.

Before coming to McGill University, Dr. Collip had an exceptionally fine training under Prof. Macallum, such as few biochemists receive who specialize. This foundation in biochemistry and physiology, combined with a knowledge of the sciences, equipped Dr. Collip to achieve results of notable character. He is an authority on the biochemistry of the endocrine system who is surpassed by few.

In order to come to McGill, Dr. Collip declined other appointments so that he might be in a position to use the opportunities and advantages placed at his disposal. While it is still too soon to forecast the results of Dr. Collip's latest discovery, it will, unquestionably, be far-reaching and redound not only to the fame of the distinguished investigator but to McGill University.

DR. CAMPBELL'S CAREER.

Dr. A. D. Campbell is a demonstrator in obstetrics and gynaecology in McGill University.

Graduating in medicine at McGill in 1911, Dr. Campbell spent two years as an interne at the Royal Victoria Hospital and then went to Western Canada, where he became a general practitioner. He was then, just before the outbreak of the war, for several months in New York studying obstetrics and gynaecology. He was also senior resident obstetrician in the New York Lying-In Hospital.

During the war he served overseas for three and a half years. In 1920 he was appointed senior demonstrator in anatomy at McGill, holding the position for seven years. For some years he has been active in the department of obstetrics and gynaecology in Montreal General Hospital, and is clinical assistant in the Montreal General and Royal Victoria Maternity Hospital. He has also been able to attend to the demands of a large private practice.

The application of the new hermone discovery and its further investigation will be in charge of Dr. Campbell in both the Montreal General and Royal Victoria Hospitals.

Assists In Work

DR. A. D. CAMPBELL, who is in charge of the clinical side and further investigation into Dr. Collip's discovery.

CANADIAN EXPORTS TO BRITAIN HIGHER

Conference of Business Men on Empire Free-Trade Urged in London

Special Wireless by J. E. Poole, The Star's Resident Correspondent.

LONDON, Feb. 14.—An address by Henry Ridpath read at a meeting today of the Canadian Chamber of Commerce urged that no policy of Empire free trade be reached without a conference of Empire business men which would be fully representative and should be held soon.

As a body the Canadian Chamber o... Commerce in London is not yet in ... position to commit itself but ... thought he could say that they we... committed to the cardinal necessity ... an effective Empire scheme wh... would involve the abandonment of ... rigid free-trade policy for a po... more in keeping with the needs of ... situation, which he hoped that ... economic conference of 1930 wo... something to solve.

He believed that public opinio... ready for action and he believ... shortly there would be a dem... action. Canada, like the ot... minions, sought a closer und... ing with the Mother Countr... the path of such an unde... there had always been a st... sistence upon a fiscal poli... to, say the least, had no... severe test of post-war co...

Mr. Ridpath pointed ou... had been substantial gr... volume of Anglo-Canadi... ports to Canada had in... per cent and Canadian ... tain had increased by ...

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New Discovery at McGill Acclaimed as Great Boon To Suffering Humanity

Both Men and Women Will Greatly Benefit by New Gland Treatment Is Found by Dr. Collip — Similar to Voronoff's Experiments

A DISCOVERY which, if first promise is realized in its ultimate development, may carry to a much more advanced stage, and in decidedly more practical form, the work that has been done in recent years by Professor Voronoff and others of his school of thought, has crowned the efforts of Dr. J. B. Collip, chairman of the department of biochemistry at McGill University and one of the co-discoverers of insulin, according to an announcement made this morning at the university.

Dr. Collip's discovery, while dealing essentially with a similar phase of human life to that which produced Dr. Voronoff's experiments, differs from the latter in several ways. It is biochemical, whereas Dr. Voronoff's researches were almost wholly surgical. Dr. Collip's treatment, while of great value to both sexes, is primarily based on treatment of women, and is destined to smooth over and facilitate every stage of development and continuation of their functions.

STIMULATE FUNCTIONS

From the moment that the child begins to turn into woman, to the moment when woman finds herself developing into matron, the appropriate functions can be stimulated, when they are sluggish, assisted when they need help, and their course in general rendered smooth and agreeable to the patient, eliminating to a very great extent the suffering and discomfort which so often characterises the various stages of life.

The discovery would appear to be based on the fact that every glandular secretion owes its peculiar effect to an active principle, which science designates as a hormone. When the hormone can be isolated from everything surrounding it which would make it difficult or dangerous to try to administer it to a patient, it can be then given to human beings, to make up for lack of that particular secretion, or penury thereof, in the body. The lack of a particular secretion is made up for, in diabetes, by injections of insulin.

First the discovery of a particular hormone, then the discovery of a secretion which will stimulate the production of this hormone, has resulted in the announcement of this new treatment, whereby organs that are sluggish or slow of development may be stimulated and assisted, and the sufferings that often accompany nature's struggle for maturity may be eliminated or mitigated to a great extent.

TAKEN INWARDLY.

The substance, developed by Dr. Collip, is not attacked by the juices of the stomach as is insulin which has to be given hypodermically. This feature, Dr. Collip points out, enables the crystalline pure extract to be given through the mouth, or by injection, at will.

A quantity of the substance has already been manufactured and is now in the laboratories at McGill. If the method of manufacture proves satisfactory additional quantities of the material will be sent out to selected university laboratories and clinics for further testing.

When asked as to the use of the substance, an authority in the medical faculty at McGill stated that the ordinary practitioner will be able to prescribe it for patients in his district. It is not expected that an individual will be well-advised to take the material without the prescription and direction of a physician.

DISCOVERED ACCIDENTALLY

The fact that the extract can be given through the mouth was discovered accidentally. Rats were used during the experiments and it was found that one of the rodents, which had in some manner obtained access to a small quantity, had eaten some of the extract.

The rat under observation showed the same effects as those treated hypodermically and further experimentation disclosed the fact that the extract was not destroyed by gastric juices.

Possibilities of a wide application of the substance are now being investigated. The thyroid gland belongs to the group affected by the hormone isolated by Dr. Collip and the extract has been found to exercise a wonderfully beneficial influence upon certain forms of goitre.

The beneficial effects of the extract are being investigated in the laboratories at McGill where research workers are highly optimistic over the results thus far obtained. Manufacture of the extract will be done at a minimum cost and the material will be available for distribution as soon as it has been fully approved by the medical profession, medical authorities at the university declared.

"It is too early to make a definite pronouncement upon the value of this treatment," Dr. Collip and his colleague Dr. A. D. Campbell, state in a preliminary report on the subject in the Medical Journal, "for numerous clinical factors have yet to be considered, as well as the question of dosage and duration of administration. It may be said, however, that definite results of a most encouraging character have been obtained in five cases of oligo-me[illegible], in two cases manifesting

...nued on Page 20

Important Find

DR. JAMES B. COLLIP,
whose contribution in connection with gland secretion is being widely acclaimed.

SMELTER'S EFFECT ON CROPS FEARED

Municipalities Gather Date on Reported Project at Ile Perrot

Active opposition to the proposal to establish a smelter for the refining of metallic ores on Ile Perrot may crystallize into joint action within a few days by a number of municipalities between Ste. Anne de Bellevue and Montreal West. At the present time a number of municipalities are said to be investigating the probable effect of fumes from the proposed smelter and, if it found that danger is likely to result, some kind of action will probably be taken.

As regards the effects of sulphur and other fumes from smelting plants, it is pointed out by a prominent engineer that in the case of a smelting plant at Sudbury, Ontario, a considerable territory surrounding the actual plant is rendered totally barren of vegetation. Also, it is pointed out that fumes from the smelter at Trail, B.C., have been the cause of governmental protest from the State of Washington to the Canadian Government. In the latter case it is claimed that farm crops in the state have been materialy damaged by the fumes from the Trail smelter. Decision in the case is pending from an international joint commission.

Without going closely into the Ile Perrot project, the engineer is of opinion that the effects of fumes from the smelter might conceivably be felt as far east as Lachine, on the Island of Montreal. Expert opinion on the subject will be collected by a number of municipalities, within the next few days, and a decision will then be reached as to future steps which may be taken.

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DISCOVERY MADE AT McGILL WILL BENEFIT WOMEN

Remedial Agent for Certain Feminine Disorders Found

REMARKABLE RESULTS

University's Medical Authorities Say Usefulness Can Hardly Be Over-Estimated

A most remarkable discovery has been made in the biochemical laboratories of McGill University by Dr. J. B. Collip, chairman of the department, and is announced by the Faculty of Medicine. It is believed that results of importance to humanity that cannot, as yet, be appraised, will accrue from the investigations which will be of particular benefit to women. An extract has been derived which offers a remedial agent for certain feminine disorders.

Clinical observation carried out by Dr. A. D. Campbell in selected cases has led to the hope that eventually results may be obtained in human beings corresponding to the experimental findings obtained in working with rodents. It is at once apparent that this discovery will be of great importance, affecting as it does almost every woman to a greater or less extent.

The discovered substance must not be regarded as a panacea for all women's disorders, Dr. Campbell emphatically explains. "Our experience thus far has demonstrated that patients should be selected, placed in hospitals and thoroughly investigated before and during the administration of this extract. It is hoped that such studies will throw new light upon the problems of ovarian dysfunction and hyperthyroidism, and, in addition, that the study of the ovary-stimulating hormone will help to unmask the aetiology of certain of the so-called toxaemias of pregnancy."

Articles by Professor Collip and Dr. Campbell appear in the current number of the Canadian Medical Journal which was issued yesterday and these give complete technical details of the discovery and laboratory experiments that have been conducted.

Dean Charles F. Martin, of the Medical faculty of McGill, made the following statement in regard to the discovery: "Professor Collip has succeeded in the purification and standardization of a hormone or internal secretion having effects somewhat similar to the anterior pituitary gland. This substance, which has been isolated in crystalline form, has been derived from the placental gland, and is of chief importance because it offers a remedial agent for certain feminine disorders by promoting maturity that has been delayed as well as by infuencing in a very remarkable manner the metabolism and general health of the patients who receive the drug.

"It further throws a very important new light on the physiological significance of the placental gland structure. A wide field for investigation has been opened up, and the McGill investigators plan to carry on thorough clinical study of the new product.

"The article in the Canadian Medical Journal by Dr. A. D. Campbell and Professor Collip illustrates their experience with this drug on human beings and the successful results of their experiments. All of this work has been based upon earlier investigations carried out in other countries, more particularly the work of Weisner of Edinburgh, and which, until the present time, had not been brought to a successful conclusion.

"The field of usefulness for this drug can hardly be over-estimated both in regard to the extent of its use and its beneficial effects. The results that have been obtained in the cases treated during experiments are reported to be most remarkable, but the investigators are reticent about declaring as yet the full value of their tests."

PRINCIPAL'S COMMENT.

Sir Arthur Currie, principal of McGill, commenting on the discovery, said:

"Everyone at McGill University rejoices exceedingly that complete success has rewarded the long and patient efforts of Professor Collip and his capable assistants in the biochemistry laboratories of our medical school. For weeks we have known of the experiments and were cheered by reports from time to time that success was in sight.

"As Doctor Martin, Dean of the Medical School, declares, it is a remarkable discovery, and should bring relief and comfort to countless thousands of women throughout the world. Discoveries that add to the material well-being of people and nations are highly desirable, but one that gives health and joy and consequent happiness to men and women deserves our everlasting gratitude."

Dr. W. W. Chipman, Emeritus Professor of Obstetrics and Gynaecology, McGill University, expressed great interest in this research. He said: "The results already secured both in the laboratories and in the hospitals thoroughly justify a strong belief in the efficacy of this new drug. Professor Collip stands already among the foremost workers in the field of biochemistry, and this recent research can but greatly add to his distinguished reputation.

"As is well known, the biochemists, both in Europe and in America, have, for some time, been engaged in the solution of this very problem. And we congratulate Professor Collip on his recent achievement.

"The clinical application of this new therapy is in the hands of Dr. A. D. Campbell both at the Montreal General and the Royal Victoria Mont-

(Continued on Page 5, Col. 6.)

the luncheon were Rev. M. F. McCutcheon, D.D., of the First Baptist Church and Rev. T. Wilson, D.D., both of the Quebec League Against Alcoholism; Mrs. T. T. George, of Toronto, and Miss Edith Giles, of Athens, Ont. The guests on the previous day were Rural Dean Saunders and Rev. Thos. Marshall, of the league. Addresses were given by the guests each day. Miss Bazin spoke on temperance in the Womens' Missionary Society. Gratifying reports were given by the various superintendents of branches.

Mrs. C. E. Enright reported for the building committee that subscriptions were being received at a satisfactory rate. Devotional exercises were conducted by Mrs. McLean, of Cushing, Que. Mrs. Arthur Reeve reported for the franchise campaign. Mrs. W. T. Colcomb and Mrs. Luttrell were delegates to the meeting on Wednesday to decide on action towards securing appointment of women police.

DISCOVERY MADE AT McGILL WILL BENEFIT WOMEN

(Continued from Page One)

real Maternity hospitals. As we learn from his article in the Medical Journal, many cases have already been treated and with excellent results. The cases deserving this treatment are to be segregated in these two hospitals under Dr. Campbell's supervision and care."

McGill medical authorities were unanimous in their enthusiasm over the discovery and in their praise of those responsible for it.

DR. COLLIP'S CAREER.

Dr. James Bertram Collip was appointed to the chair of biochemistry in the medical faculty of McGill University in the fall of 1927. He graduated with special honors in physiology and biochemistry in the University of Toronto in 1911 and shortly after entered a graduate course in these subjects, receiving his Ph.D. degree in 1914.

After graduation he accepted an appointment as lecturer in biochemistry at the University of Alberta, obtained his doctorate of science in that institution and was later appointed to a professorship. He obtained his M.D. later and was elected to a fellowship in the Royal Society of Canada.

Although somewhat under forty years of age, Professor Collip has become recognized as one of the leading biochemists in America. H won his first outstanding laurels connection with the discovery insulin when he was associated Dr. Frederick G. Banting and Charles H. Best in this work. was one of the recipients of the of money accruing from the N prize awarded to Dr. Banting Professor MacLeod.

Since that time, 1922, Dr. C has done notable work in conne with parathyroid glands, the a principles of which he has disc ed and isolated. As an auth on the biochemistry of the endo system in particular Professor C has few equals. He was a stu under Professor Macallum and h training such as few biochem have had before specializing. knowledge of the sciences wit foundation in physiology and chemistry has enabled him to ach results of an outstanding chara

FAR-REACHING RESULT

Doctor Collip refused a numb other appointments in order to to McGill, and he has been a make signal use of the opportu and facilities at his disposal. results of his latest discovery, th still difficult to foresee, are b to be far-reaching and will world-wide renown upon this inv gator, and also to McGill Univer

Dr. A. D. Campbell is a der strator in Obstetrics and Gynaeco at McGill University; clinical as ant at the Montreal General Royal Victoria Maternity Hospit He graduated in medicine at Mc in 1911 and spent two years as interne at the Royal Victoria Hospital. He then went out to Western Canada where he became a general practitioner. Just prior to the war he spent several months in New York City studying Obstetrics and Gynaecology. He was senior resident obstetrician at the New York Lying-In Hospital.

After serving overseas for three and a half years, Dr. Campbell was appointed senior [illegible]strator in anatomy at [illegible] tion he [illegible] has b[illegible] Ob[illegible] M[illegible]

IMPORTANT DISCOVERY AT McGILL UNIVERSITY

The current number of the CANADIAN MEDICAL ASSOCIATION JOURNAL announces, in the form of a preliminary paper, a remarkable discovery in the Biochemical Laboratories of the Medical Faculty.

It appears that Professor J. B. COLLIP, head of the Department of Biochemistry, has succeeded in the purification and standardization of a hormone or internal secretion having effects somewhat similar to the anterior pituitary gland. This substance, which has been isolated in crystalline form, has been derived from the placental gland, and is of chief importance because it offers a remedial agent for certain feminine disorders by promoting maturity that has been delayed, as well as by influencing in a very remarkable manner the metabolism and general health of the patients who receive the drug.

It further throws a very important new light on the physiological significance of the placental gland structure. A wide field for investigation has been opened up, and the McGill investigators plan to carry on a thorough clinical study of the new product.

A second article in this same Journal, by DR. A. D. CAMPBELL and Professor COLLIP, illustrates their experience with this drug on human beings and the successful

results of their experiments. All of this work has been based upon earlier investigations carried out in other countries, more particularly the work of Wiesner of the University of Edinburgh, and which until the present time had not been brought to a successful conclusion.

The field of usefulness for this drug can hardly be over estimated, both in regard to the extent of its ~~benefit~~ use and its beneficial effects.

One should add that, while in the few cases concerned, these results are remarkable, the investigators are reticent about declaring as yet the full value of their tests.

Twelfth February, 1930.

Everyone at McGill University rejoices exceedingly that complete success has rewarded the long and patient efforts of Professor Collip and his capable assistants in the Bio-Chemistry Laboratories of our Medical School. For weeks we have known of the experiments and were cheered by reports from time to time that success was in sight.

As Dr. Martin, Dean of the Medical School, declares, it is a remarkable discovery, and should bring relief and comfort to countless thousands of women throughout the world. Discoveries that add to the material wealth of people and nations are highly desirable, but one that gives health and joy and consequent happiness to men and women deserves our everlasting gratitude.

The Canadian
Medical Association Journal

Vol. XXII TORONTO, JUNE, 1930 No. 6

FURTHER OBSERVATIONS ON AN OVARY-STIMULATING HORMONE OF THE PLACENTA*

BY J. B. COLLIP,

Department of Biochemistry, McGill University,

Montreal

INTRODUCTION

AS has been stated in preliminary communications[24, 25] on this subject, the writer became interested in the problem of the isolation of the œstrogenic hormone from the placenta after a visit to the Biochemical Laboratories at McGill University of Dr. B. P. Wiesner, of the Department of Animal Breeding, Edinburgh University. Dr. Wiesner very frankly laid the problem before us and urged us to undertake research in this field. The result of our investigation, which will now be given in detail, may be said to be built upon and to be the outcome of the earlier work of Wiesner and his collaborators.

LITERATURE

It has long been known that the placenta contains a substance capable of producing œstrus changes in the uterus and vagina of oöphorectomized animals, and to this extent duplicates the endocrine function of the ovary.[55] As recent reviews of the properties of this substance (œstrin)[53, 79] and of the physiology and pathology of the placenta[72] are available, only the more important characteristics need be mentioned. Œstrin is lipoid-soluble but not insoluble in water; it is not destroyed by high temperatures, nor by acids nor alkalies; and is not inactive when administered orally. With few exceptions[57, 100] workers are agreed that it has no stimulating action on the ovary.

Hirose, in 1920,[59] demonstrated that intraperitoneal injections of a suspension of placenta produced in rabbits marked changes in the ovaries, especially the appearance of numerous corpora lutea; this effect was not obtainable with acetone or ether extracts. Placenta was found to be active only in the first half of pregnancy. This paper has not been accessible to us, and we have found it quoted only by Murata and Adachi[74] who confirmed and greatly extended its conclusions. They found that the enlargement of the uterus noted by Hirose could not be produced by this technique in oöphorectomized animals, and concluded that it was due not to the œstrin content of the injected material but to the secretion of œstrin by the ovary.

In the meantime attention had been directed to the anterior hypophysis. Evans and Long,[39, 40] in producing gigantism in rats by continued massive injections of saline extracts of this tissue, had noted a suppression of the œstrus cycles and an accumulation of lutein tissue in the ovaries; ovulation in the hen was similarly suppressed.[109, 75] But experiments in grafting[52] and parabiosis[71, 50] suggested that an ovary-stimulating substance circulated in the blood even of castrated animals, and Zondek and Aschheim set themselves to discover its source. They found[113, 114, 115] that intramuscular implantations of small amounts (10-20

* Received for publication on April 24, 1930.

mgm.) of macerated anterior hypophysis into immature female mice led rapidly to the premature appearance of puberty, as judged by the ripening of follicles and ovulation, formation of corpora lutea, and an outpouring of œstrin, demonstrated by the opening and cornification of the vagina and the enlargement and hyperæmia of the uterus. Similar results were independently obtained by Smith and Engle[95, 96, 97] with rats, the observed superovulation being especially remarkable. None of these effects could be produced in oöphorectomized animals.

These findings have been confirmed repeatedly.[17, 18, 20, 41, 49, 70] The active principle appears to be present in the anterior hypophysis at all ages[88, 89, 92, 93, 94, 66] and in male animals and castrates to an extent greater than in normal females;[42] in pregnancy, the amount present decreases.[10, 81] It is present also in other human tissues, as in the decidua and the placenta (implants of 0.1 gm.), especially in the first half of pregnancy,[81] in the corpora lutea of pregnancy, and in the blood and urine from an early stage in pregnancy till some days after parturition.[3] It is not demonstrable in blood or urine at other times, except occasionally in infants,[21, 80] nor regularly in amniotic fluid,[21, 81] nor in cerebrospinal fluid during pregnancy.[48, 99, 31] These results led Aschheim and Zondek[4, 8, 9] to suggest the injection of one or two c.c. of urine into immature mice as a test for pregnancy. They describe three reactions which may follow: (1) development of follicles and œstrous changes in the vagina and uterus; (2) hæmorrhages into the follicles, usually visible macroscopically: (3) formation of corpora lutea, chiefly atretic. These reactions are not specific for pregnancy, as they may be obtained with urine from cases of various endocrine disorders, tumours, or inflammatory lesions,[6] or in amenorrhœa, or at the menopause.[32] Reactions 1 and 2, however, permit a diagnosis of pregnancy from the second month onwards, and give correct results, positive or negative, in about 97 per cent of the cases, as other workers have also found.[69, 30, 63, 106] Positive results have also been obtained with the urine in pregnancy in apes[30] and monkeys, but not in the cow, sow, rabbit, or mouse.[30] Active extracts have been prepared from the anterior hypophysis, and from the human placenta or urine of pregnancy.[118, 17, 85, 41] It is frequently impossible to discover from the writings of the German workers the source of the material used, and it has been universally assumed that the active principle is the same in each case. Evans and Simpson[43] however, point out that while the increase in size of the ovary is roughly proportional to the amount of hypophyseal material implanted, no such linear relation can be discerned with injections of varying amounts of urine of pregnancy.

Injections of such extracts into immature mice (3 to 4 weeks, 6-8 gm.) or rats (4 to 5 weeks, 30-35 gm.) produce effects similar to those of the solid implants, except that ovulation is seldom if ever observed,[37, 123] and the tendency to atretic luteinization and hæmorrhage is greater. The outpouring of œstrin leads to the uterus becoming distended and hyperæmic; the vaginal smear shows cornified cells and an absence of leucocytes, and the blood cholesterol probably rises.[86, 119] The unit is usually taken as the amount which, divided into six doses, produces signs of full œstrus in about 100 hours in such immature rodents. Mice are absolutely as well as relatively less sensitive than rats.[119] The absence of œstrin must be demonstrated by negative results with oöphorectomized animals; the weight of evidence[93] is against the view that an œstrin effect may be obtained with anterior hypophysis. Copulation may take place during such premature œstrus,[96] but the age at which the animals first become pregnant is not reduced.[33] If the injections are continued, the ovary enlarges to ten times the normal size, and consists almost wholly of corpora lutea, the majority of which are atretic and often hæmorrhagic. The cyclic changes in the vagina may persist for some time[18] but tend to disappear, and the epithelium passes into a secretion phase with a high mucous layer, while the uterus is no longer distended, but its muscular layers are hypertrophied.[121, 73]

These effects may be ascribed to the internal secretion of the corpora lutea,[26, 111] the activity of those produced by this treatment having been demonstrated by the deciduoma reaction.[103, 74, 19, 44] This hormone itself may be present in the placenta.[61] The luteinization and enlargement of the ovaries are also conspicuous in mature animals, though superovulation may still be produced by implants.[96, 34] In the ovaries of pregnant mice[117]

or rabbits[74] the formation of new corpora lutea may be evoked, in some cases certainly preceded by ovulation, without disturbing normal parturition. This is not a constant finding[92] and in other hands extracts of anterior hypophysis[102] or placenta[44] have impaired the birth mechanism or[35] produced abortion or reabsorption of the fetuses. Immature male rodents react less strikingly to treatment of this kind than do females; there is accelerated development of the seminal vesicles and accessory glands, to a lesser degree of the penis and testes;[96, 107, 121, 18] the endocrine activity of the testes is said to be increased,[101] but spermatogenesis may actually be inhibited.[16, 36] In doves, however, the testes may be very greatly enlarged after implantation or injection of glycerol extracts of anterior hypophysis.[87] The ovaries of senile female mice may be reactivated so that œstrus cycles may reappear,[118] but when implants were made into mature mice, which for unknown reasons showed no œstrous cycles, the first induced œstrus was not followed by renewed cyclic activity.[67]

In rabbits, ovulation following the injection of extracts of anterior hypophysis has been observed,[14] but the formation of lutein cysts in the ovary[54] appears to follow; this latter change has also been seen in dogs.[17, 86] Implants made into apes may stimulate follicular growth,[2] or may produce enlargement of the uterus without visibly affecting the ovaries;[29] several workers, however, have insisted on the independence of the endocrine activities of the ovary.[78, 116, 110] In human subjects, implants failed to induce menstruation in a case of delayed puberty, or after the menopause, but good results were obtained in the treatment of various menstrual disorders[28] and soluble preparations have also been used with some success;[17, 120, 60, 76, 91] hyperæmia and hyperthermia in the pelvic region may be noted, but not invariably.[22] Since in the case of hydatid mole and malignant chorionepithelioma the pathological tissues[74, 5, 51, 90] and the urine[5, 122, 77] contain large quantities of the hormone, an explanation of the frequent appearance of lutein cysts of the ovary in these conditions, or in the presence of hypophyseal tumour,[108] seems not far to seek.

The most widely known of the chemical characteristics of the hormone is its instability; it is destroyed by boiling and injured at 60°C., or by exposure to strong acids or alkalies,[118, 17] or to digestive enzymes,[56] and in consequence is ineffective when given by mouth, except in very large doses and under the most favourable circumstances.[119, 56, 98] It is diffusible and dialyses rapidly, a fact which may be taken advantage of in its preparation.[118, 17] It is said to be soluble in water or dilute acids, but insoluble in fat solvents, and is purified[119] by precipitating it from aqueous solution by the addition of alcohol. We have not been able to find specific claims of the maximum potency and concentration obtainable by such means; commercial preparations may contain 50 rat units per c.c., but are decidedly toxic.[47] Dickens[27] has described a new preparation from the urine of pregnancy by precipitation with saturated ammonium sulphate and subsequently with tannic acid. His preparation is active in doses of 0.01 mgm. by injection, is not destroyed by pepsin or trypsin, but is unstable in acids or alkalies, and is insoluble in alcohol. Where œstrin is present in the original material (placenta or pregnancy urine) it is usually removed by extraction with ether or some other fat-solvent; we do not feel confident, however, that a quantitative separation has always been obtained in the preparation of either fraction.

Alkaline extracts of the anterior hypophysis promote growth[45, 82] and acromegalic and splanchnomegalic distortion,[84] with enlargement of the gonads,[105] and temporarily lower the non-protein nitrogen of the blood,[104] while they produce extensive luteinization in the ovary and lead to a suppression of œstrus;[41, 78, 54, 62] extracts made with dilute acid, however, are not growth-promoting,[64] but promote premature puberty,[41, 83, 12, 13, 58, 17, 110] yet they are not free from the tendency to cause luteinization, and to impair the birth mechanism; this is also true of the extracts from placenta or urine, which are devoid of growth-promoting power.[41, 44, 112, 73] Evans believes that the alkaline extracts actually antagonize the puberty-accelerating effect of acid extracts or of implants.[41] That the ovarian response to implants, to acid hypophyseal extracts, or preparations from placenta or urine, may take the form either of follicular or of luteal development has been regarded by many workers[17] as a question

of dosage, or[13] of the initial stage of the ovary. Amongst those[21] who believe that two distinct hormones are concerned, Wiesner[110, 112] has taken a leading position. He distinguishes "Rho-one", which stimulates the secretion of the œstrin, the maturation of follicles and the formation of corpora lutea, from "Rho-two" which maintains the corpus luteum in activity and stimulates it to internal secretion.[111, 73] Extracts of either anterior hypophysis[110] or placenta,[112] made with sulphosalicylic acid, contain both principles (an ingenious hypothesis is offered to explain the predominance of one or the other, according to dosage), but as "Rho-one" is totally destroyed by heating to boiling for one minute, while "Rho-two" in part survives such treatment,[112, 74] a clear separation can be obtained.

Mucification of the vagina in immature rats is the test by which "Rho-two" is assayed; this appears in sections, but is not detectable by the smear technique. Claus[23] has obtained from the anterior hypophysis a microcrystalline substance insoluble in absolute alcohol which promotes premature puberty and ovulation in female rodents; the potency is not stated but a great loss of activity is apparently involved in the preparation. A fraction soluble in absolute alcohol produced luteinization; the physiological effect of unresolved mixtures is dependent on the dose. Aschheim[7] pointed out that certain urines gave reaction 1, *i.e.*, œstrus, but never gave reactions 2 or 3, *i.e.*, hæmorrhagic follicles and luteinization. Zondek[123, 124] has now accepted the view that two hormones are concerned, "Prolan A", which causes œstrin secretion, and "Prolan B", which is assayed by the appearance of corpora lutea in the ovaries of immature mice; he claims, also, to have obtained "A" free from "B" from the urine of non-pregnant women, especially after natural or artificial menopause. The significance of the follicular hæmatomata is obscure; Fellner[46] regards the phenomenon as due to a non-specific, irritant impurity.

The relation of the placenta to the anterior hypophysis in this system remains obscure. Placental extracts induce in the hypophysis histological changes[1, 15, 65] similar to those seen in pregnancy,[38] but this may be due merely to œstrin.[11] Zondek,[122] like Philipp,[81] is inclined to believe that the placenta does not merely collect and store the hormone produced by the anterior hypophysis, but takes an active part in the production; but he maintains that the flooding of blood and urine with the hormone takes place so early in pregnancy that it must be ascribed to hypophyseal, not to placental, activity.

METHODS

Sulphosalicylic acid was employed in the first instance as an extracting agent, and it was used in the manner described by Wiesner.[110] Fresh or recently collected human placentæ were used. It was also found that frozen placentæ could be used and that the process of freezing did not materially affect the yield of active extract.

It was found that the injection of dilute sulphosalicylic acid extract into immature rats consistently produced the phenomenon of premature maturity. While attempts were being made to concentrate this extract and at the same time remove the sulphosalicylic acid without loss of potency (a result which was not achieved), it was decided to make some preliminary trials with acetone and alcoholic extracts of the fresh placenta. Dr. Wiesner had told us that he had had no success in the use of alcohol or acetone in the making of potent extracts, and in his recent paper he has emphasized this fact. However, it has been our experience that extraction of the material with neutral or faintly acidulated alcohol or acetone yields at once an extract which is invariably potent. When this fact had been thoroughly established it was decided to abandon the sulphosalicylic acid extraction process, and to develop a standard technique based upon the preliminary treatment with acetone or alcohol. Numerous attempts were made to fractionate these simple extracts and to recover the maximum amount of active substance in some one fraction. It should be added here that we had convinced ourselves at the outset that we were not dealing with œstrin. This factor has been carefully controlled by repeated extraction of our extracts with ether before submitting them to assay, and also by the use of proven oöphorectomized rats. These latter animals have been shown to be reactive to œstrin both before and after treatment with the œstrin-free placental ex-

tracts, and they have given uniformly negative responses to such extracts.

One process which has been found to give excellent results, making use of human placenta, is as follows:

The placental tissue is finely pulped and treated with either one and one-quarter volumes of acetone or two volumes of 95 per cent ethyl alcohol. When one is using alcohol as the extracting vehicle one may with safety add several volumes of this reagent to the freshly ground glands, as the active principle which one wishes to obtain appears to be soluble in all strengths of grain alcohol. The mixture is kept agitated for some time and is then allowed to stand at room temperature for twenty-four hours. The fluid content is next separated from the mixture by the use of a suitable press. It is filtered, and to the filtrate one adds one-half c.c. of glacial acetic acid per litre. The reagent, acetone or alcohol, as the case may be, is removed by distillation at low temperature and reduced pressure. Concentration of the aqueous phase is continued until one has obtained a volume equal to one-half that of the placental tissue originally extracted. A filtering agent is now added to facilitate rapid filtration and to remove by adsorption a certain amount of undesirable material. An acid-washed hydrated aluminum silicate, such as Lloyd's reagent, has given excellent results in our hands. The filtrate is returned to the still and very cautiously concentrated under reduced pressure to the consistency of a thin syrup. Ten volumes of alcohol, either absolute or 95 per cent strength, are added. It is important that the alcohol be added very slowly and that the mixture be kept violently agitated during the process. The purpose of adding such a quantity of high grade alcohol at this stage is to remove by precipitation undesirable material and to retain in alcoholic solution the bulk of the active principle. It may be noted that herein our process differs materially from other processes which have been suggested for the purification of maturity-producing factors.

The mixture of concentrate and ten volumes of alcohol may be placed in a freezer at a temperature of –10°C. for several hours. This, however, is not an essential step. The mixture is next filtered and the residue may be again extracted with hot alcohol and the extract thus obtained filtered and added to the first extract. The combined filtrates are then concentrated under reduced pressure to a thin syrup and again treated with alcohol, preferably absolute, in the manner above described. The mixture is filtered and again concentrated to remove all traces of alcohol. The aqueous mixture remaining in the still is diluted with sufficient distilled water to allow of the extraction of lipoids by ether. This is done in a separatory funnel in the usual manner. The process of ether extraction should be repeated at least five times. The ether is removed from the aqueous solution by distillation at reduced pressure and the concentration process is then continued until the material in the distilling flask is almost dry. (An aqueous or dilute alcoholic solution of the product at this or an earlier stage—as, for example, after one treatment with ten volumes of alcohol followed by the removal of œstrin by ether—has been found to be satisfactory for most clinical needs). The residue is then extracted several times with small amounts of absolute ethyl alcohol.

The combined alcoholic extracts are filtered and the filtrate is made strongly ammoniacal by the addition of one-third volume of saturated aqueous ammonia. The mixture is placed in a crystallizing dish and allowed to concentrate by slow evaporation at room temperature. Several days may be allowed for this stage and small amounts of ammonia and alcohol may be added from time to time as indicated. The semi-crystalline solid material which separates out may be separated from the mother liquor and washed three times with dilute cold aqueous ammonia. The washed solid material is then extracted with hot absolute alcohol faintly acidified with glacial acetic acid. The alcoholic extract is treated with one-third volume of saturated aqueous ammonia and set aside. The solid material which separates is again treated as outlined above. One then obtains the final product by chilling the absolute alcohol extract of the above substance.

The precipitate from alcohol may be further purified by repeated solution in hot alcohol and separation by chilling of the filtered alcoholic solution. The purified product is relatively insoluble in water, and indeed its

separation from an alcoholic solution can be greatly facilitated by the addition of distilled water in amount sufficient to reduce the alcoholic concentration to 50 per cent, or even lower.

Some success has also been had with a modified procedure. The principle involved in this modification of the above method consists in the adsorption of the hormone upon calcium phosphate. In this method, therefore, one can work with very dilute aqueous solutions of the placental hormone, and to a large extent shorten the somewhat tedious process with alcohol. One adds to a known potent aqueous solution of the placental hormone, which has been freed of protein and lipoid substances, sufficient neutral sodium phosphate solution to give a concentration of 0.2 per cent. The solution is then made strongly ammoniacal, and 5 per cent calcium chloride solution is slowly added. The mixture is stirred vigorously during the addition of the calcium chloride, enough of which should be added to precipitate all of the phosphate. The precipitate is recovered, washed with dilute ammonia and then extracted at least three times with hot 95 per cent or absolute alcohol which has been faintly acidulated with glacial acetic acid. The alcoholic extracts are combined, filtered, and concentrated to a small volume. The active principle may then be purified from this solution as indicated in the previous paragraphs.

Properties of the Purified Substance

As we have as yet been unable to obtain more than a few milligrams of the purified hormone at any one time, it is impossible in this communication to define with accuracy very much of the chemical properties of the active principle. The yield of the final purified product which has been obtained has been of the order of 1 mgm. per kilo of original placenta. The potency of an active extract has not been appreciably affected by boiling for five minutes in dilute acetic acid solution. We have, however, evidence of deterioration of the saline solution of the purified product. There has been such an urgent demand for the active extract for both laboratory and clinical experiments that the preparation of a sufficiently large sample of the purified product for chemical study has had to be postponed. This investigation is, however, about to be continued, and it is hoped that one will be able to publish a detailed report of such a study very shortly.

Physiological Effects of the Active Principle

The only physiological effect of the hormone which we have been able to study in a quantitative manner has been the production of premature maturity in immature rats or mice. Rats have been used almost entirely for the detailed studies. Also it has been found best to use rats three weeks of age and under 35 grams in weight. In the early stages of the investigation the experimental animals were sacrificed five to seven days after the initial injection, and the vagina, uterus, and ovaries were sectioned and studied microscopically. The positive animals manifested the changes in the uterus and vagina usually associated with œstrus, but in addition the ovaries were enlarged, and on section corpora lutea were usually found as well as normal follicles in varying degrees of development. Later it was found satisfactory to use the vaginal smear method in routine testing of extracts. It has been our practice to make injections twice and at twenty-four hour intervals, the same amount of extract being administered on each occasion. The injections were made subcutaneously and the puncture sealed immediately with collodion. Vaginal smears were taken daily, starting on the third day (72 hours). An epithelial or squamous cell flush occurring up to the sixth day has been arbitrarily read as a positive. One may have some evidence of a positive reaction as early as the third day.

It is also of interest to note that corpora lutea have been seldom found in the ovaries of immature rats which have been treated with either a fraction soluble in 85 per cent alcohol or the recrystallized final product. This observation lends a considerable measure of support to the hypothesis of Wiesner that there is a separate principle which stimulates luteinization. The suggestion which was made in a preliminary paper[24] that the finding of corpora lutea in the treated animal might be made the basis of a test for active extracts of the hormone which we are studying is therefore untenable.

It having been established that the immature rat was a satisfactory test animal for the deter-

mination in a rough way of the potency of various extracts, it was deemed advisable to undertake a series of experiments to determine the effect of excessive dosage of the hormone upon both normal and pregnant animals. Up to this time we had tentatively accepted the hypothesis that the maturity-provoking factor of the placenta was identical with the anterior-pituitary gonad-stimulatory principle. As the investigation proceeded, however, it became apparent that a theory according to which the placenta is considered as the ductless gland of pregnancy, producing by an active process a pregnancy hormone with both physiological and chemical properties peculiar to itself, would fit the observed facts much better. While we do not feel that we have as yet sufficient evidence available to prove this theory conclusively, we are nevertheless of the opinion that there are many observations which support it. Some of this evidence may now be considered.

1. Extracts which have been prepared from anterior pituitary lobes by the use of acetone, as in the case of placenta, have been found to be non-œstrogenic in character. These extracts have been prepared from small amounts of tissue. It is possible, however, that by the use of large amounts of these glands an active principle similar to that herein described may be obtained.

2. It has been repeatedly shown that the placental œstrogenic hormone is effective by the oral route, and it is proposed ultimately to standardize the extract which may be made available for clinical use in terms of oral rat units.

3. Considering the limitations of accuracy in potency testing with a limited number of immature rats, we have observed no decrease in potency following treatment of active extract with either pepsin or trypsin.

4. The prolonged treatment of normal adult rats with large doses of the hormone has not resulted in any noticeable effect upon the cycles or upon impregnation or lactation. Moreover, such treated rats have shown no evidence of marked hypertrophy of the ovaries, nor has there been any evidence of superfetation. Abortion has not been produced. The hormone viewed as a pregnancy principle could not of course be expected to cause abortion.

The following condensed protocols of four experiments are of interest in this connection:

Rat No. 1: Weight 191 grm.

Nov. 8. Started daily injection of 50 per cent acetone extract = 3 grm. human placenta.

Nov. 14. Litter.

Dec. 4. Injections every second day.

Dec. 20. Male placed in cage.

Jan. 11. Equivalent of 5 grm. of placenta (85 per cent alcohol soluble) injected every second day.

Jan. 16. Litter (7).

Feb. 12. Male placed in cage.

March 17. Weight 187 grm. Killed for microscopic study of genital tract. Ovary normal (see Fig. 6).

Rat No. 2: Weight 175 grm.

Nov. 8. Started daily injection equivalent to 3 grm. human placenta.

Nov. 18. Litter (6).

Dec. 4. Injection every second day.

Dec. 20. Male placed in cage.

Jan. 11. Litter (8). Standard injections, equivalent to 5 grm. of placenta, every second day.

March 21. Weight 176 grm. (See Chart 1, No. 14, for cycles).

Rat No. 3: Weight 137 grm.

Nov. 6. Started daily injection equivalent to 3 grm. of placenta.

Dec. 7. Injections every second day.

Dec. 24. Male placed in cage.

Jan. 11. Equivalent 5 grm. of placenta every second day.

Jan. 31. Litter.

Feb. 4. Eating poorly.

Feb. 26. Injections stopped on account of poor condition of animal.

March 8. Dead of respiratory infection. Weight 91 grm. Ovaries normal. (See Chart I, No. 13, for cycles).

Rat No. 4: Weight 136 grm.

Nov. 6. Started daily injection equivalent to 3 grm. placenta.

Dec. 6. Injection every second day.

Dec. 24. Male placed in cage.

Jan. 11. Equivalent 5 grm. placenta every second day.

Jan. 16. Litter (8).

Feb. 10. Male placed in cage.

March 10. Litter (7).

March 21. Weight 200 grm. Normal.

Also Charts 1 and 2 show the results of 17 experiments in which the hormone was administered daily or bi-daily, and in varying dosage. In general it may be said that we have little or no evidence of any interference with the normal sex functions in normal adults as a result of treatment with even massive doses of this hormone.

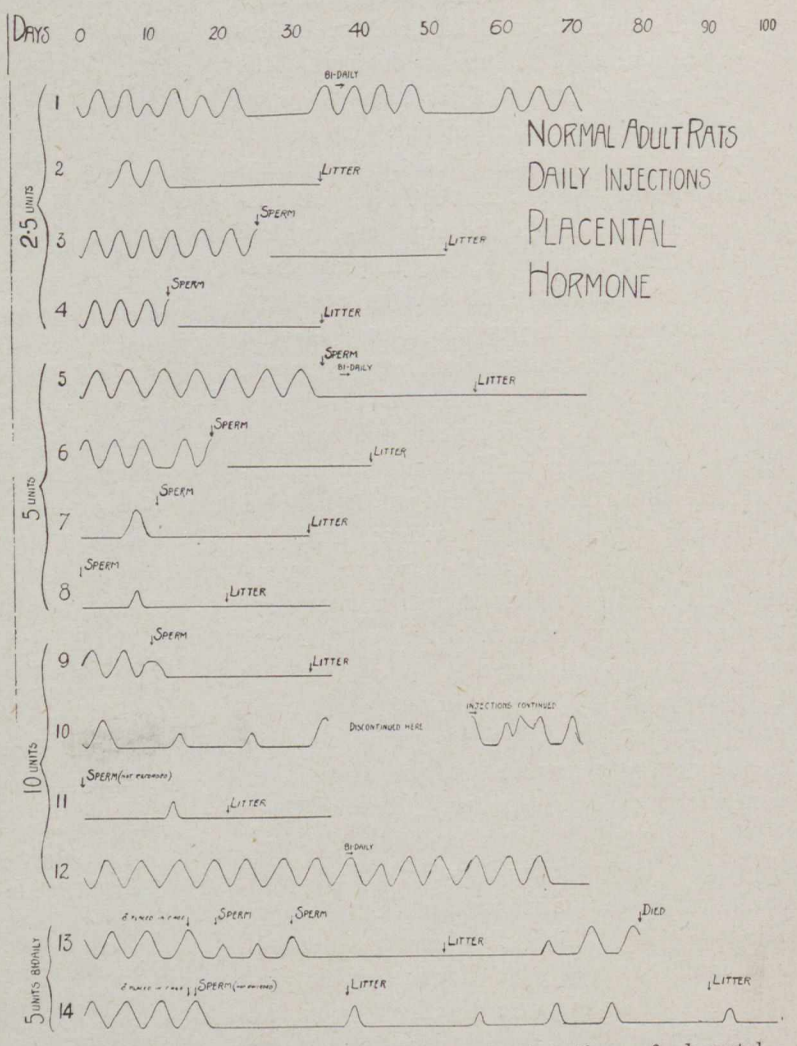
Normal rabbits and dogs, both male and female, have been injected daily with varying amounts of the active extract, up to 100 rat units in the case of rabbits and 200 rat units in the case of dogs, and frequent blood chemistry studies have been made on such animals up to one month. Apart from slight to moderate increases in the cholesterol content, which, however, we hold to be a non-specific action, nothing of significance has been observed in the chemistry of the blood.

Normal female dogs and rabbits have not manifested any appreciable degree of hypertrophy of the ovaries when treated with the hormone. It is of interest to note that in such animals there has been no sign of luteinization of the ovaries, which on section have been found to be very rich in follicles in various stages of development (Figs. 1 and 2).

We have noted that immature rats which have been brought to a state of premature maturity by the treatment with the hormone commence at once, as a rule, to manifest the cyclic changes. This has occurred both in animals receiving the usual assay treatment and in others which have been injected daily for several weeks.

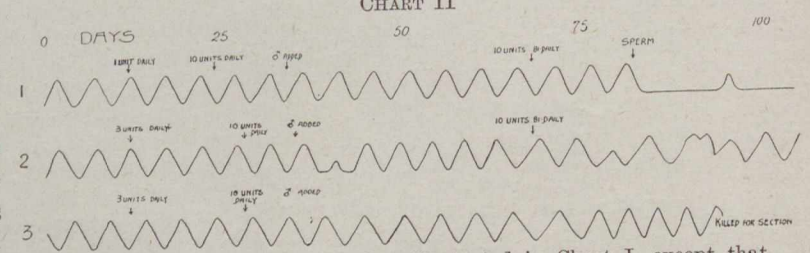
We have recovered sperm in a great many instances from the vagina of treated immature rats and have many examples of successful impregnations, associated with normal gestation, birth, and the rearing of litters. In no case, however, has impregnation occurred coincident with the first cycle. The earliest instance of impregnation which we have observed has been the third cycle, and here the young were born on the 62nd day of life of the mother. Some of these young mother rats have had difficulty in adequately nursing their young, while others have reared average weight litters. Since the purified hormone has been used we have not observed the formation of corpora lutea in association with the first cycle. These may be observed at later cycles, however, and one is tempted to associate failure of impregnation in our experience at the

CHART I



Showing the effect of daily or bi-daily injections of placental hormone into normal adult female rats caged with males. The unit used here was the equivalent of one gram of fresh human full term placenta.

CHART II



A similar experiment to that illustrated in Chart I, except that preliminary control periods are shown. Rat No. 3 had normal ovaries.

first cycle with absence of the luteal phase. Long and Evans[68] have stated that the first cycle may be a non-fertile one. Fig. 3 and 4 represent sections of the ovaries of two immature rats brought to maturity with the hormone treatment. Each was sacrificed at the first œstrus period. Corpora lutea are absent in the first ovary and present in the second. The first animal received an absolute alcohol soluble fraction, the second a 50 per cent acetone extract. Corpora lutea may not be found in certain animals even after the second cycle.

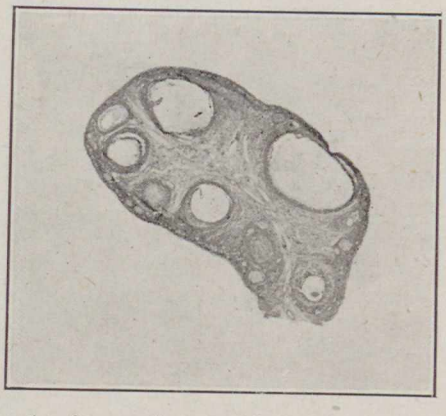


FIG. 1.—Ovary of the adult rabbit after 21 daily injections of 80 units. Note the absence of corpora lutea.

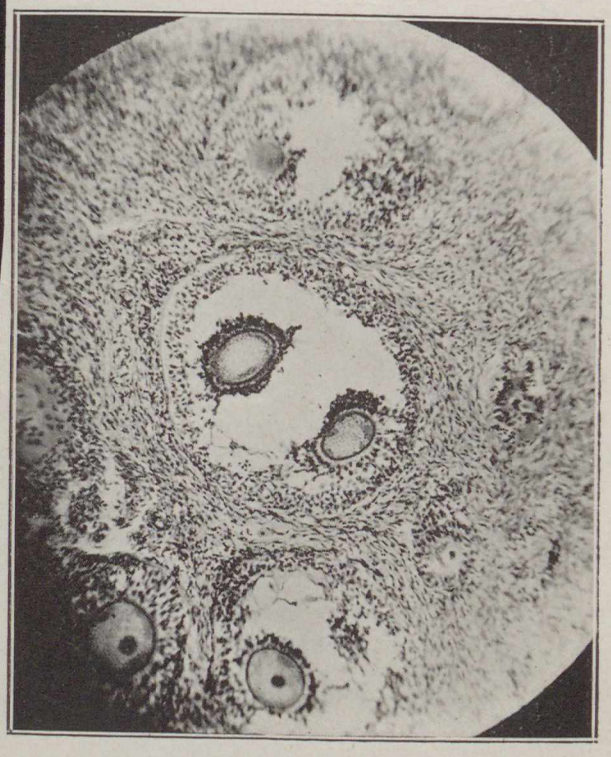


FIG. 2.—Ovary of female dog 4 days after 200 units daily. Note the absence of corpora lutea. Twin ova are seen in a single follicle.

We have noted, in our rat colony, some exceptions to the general type of cycle, which it may be of interest to mention at this time. We have had one rat which was given the equivalent of one gram of placenta daily, starting at 26 days of age, and 34 grams in weight. This animal manifested a continuous cornification of the vagina for 17 days. The injections were stopped and a state of diœstrus was instituted which lasted until injections were resumed 28 days later. Cornification of the vaginal mucosa reappeared and was continuous for 12 days, at which time injections were again stopped. The animal was sacrificed 8 days later and the ovary was found to be of normal size and free of corpora lutea.

In another instance a senile rat which was studied daily by the vaginal smear method showed a continuous cornification phase. After

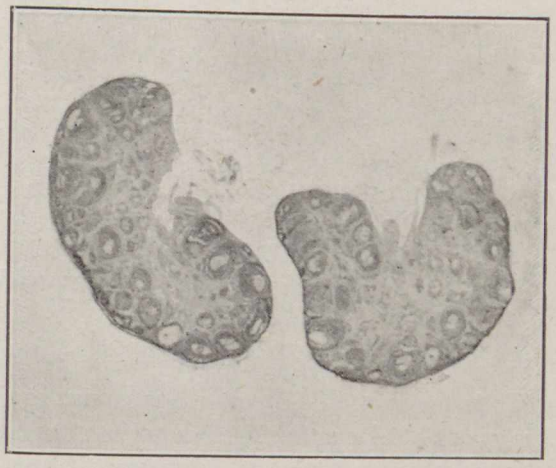


FIG. 3.—Ovaries of a rat 27 days old, 30 grm. Injected with alcohol soluble fraction in potency test. Strong positive reaction. Killed on the fifth day. Note the mild hypertrophy and wealth of follicles. Corpora lutea absent.

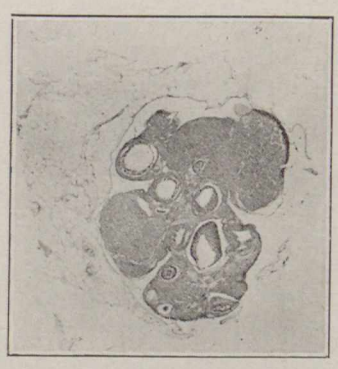


FIG. 4.—Ovary showing corpora lutea. Rat 28 days old; 37 grm. weight. Injected with the equivalent of 3 grm. placenta, as a relatively crude extract made by use of 50 per cent acetone.

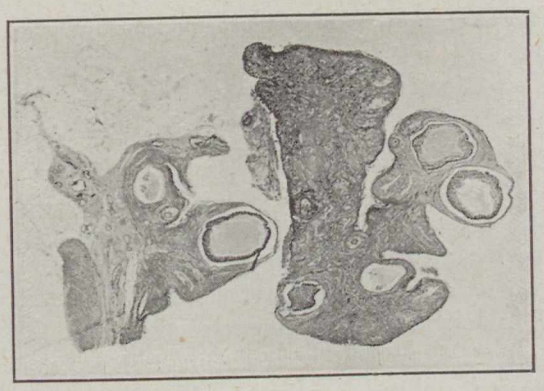


FIG. 5*a*

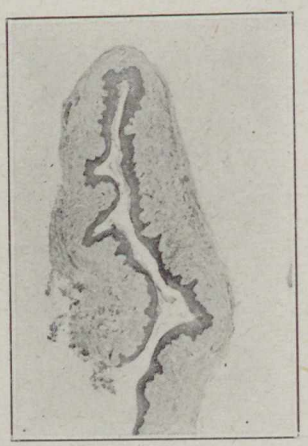


FIG. 5*b*

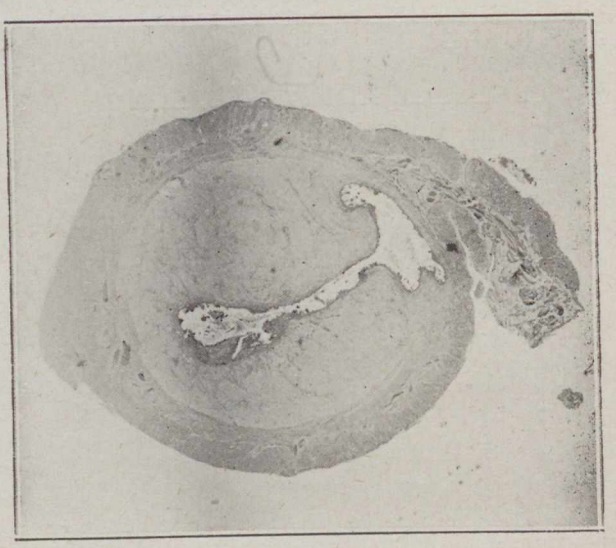


FIG. 5*c*

Senile rat in continuous œstrus. *a*. Ovary. *b*. Vagina. *c*. Uterus. Note cystic follicles in ovary, also hyperplasia of mucosa of uterus.

six weeks' observation the hormone was administered for one week in daily doses the equivalent of five grams of placenta. The animal continued to show daily squamous cell flushes. It was killed at the end of a week and no corpora lutea were found in the ovary. The follicles appeared cystic in character while the uterus was tremendously hypertrophied (Fig. 6).

These two rare examples of abnormal cycles in the rat are quoted because of the parallelism with certain clinical types of ovarian dysfunction which is suggested.

DISCUSSION

It has been our endeavour in this research to secure placental extracts free from œstrin, and also free from specific luteinizing factors. The active principle, while manifesting the property of a specific stimulant to the immature rodent ovary, causing it to develop to a mature state and to assume thereafter the normal cyclic function of the post-puberty state, should, we feel, be considered a pregnancy hormone. Our conception of the physiological significance of this active principle is that it is produced in the placenta throughout pregnancy for the specific purpose of assuring the continued functioning of the ovary. There is now ample evidence to show that both œstrin and the corpus luteum hormone are produced by the ovary during pregnancy and that ovulation is inhibited. That there must be other

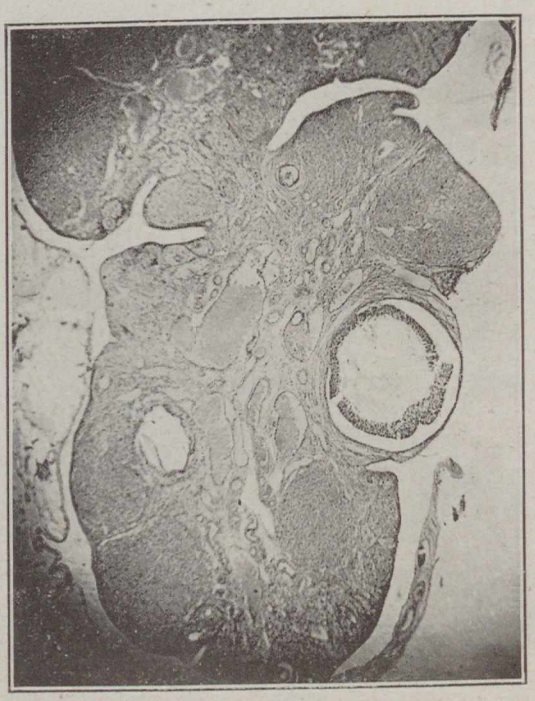


FIG. 6.—Ovary of Rat No. 1, killed after two pregnancies. (See protocol for details).

factors, such as anterior pituitary influence playing an active part in the hormonal balance during this state, is freely admitted. Although it has been proved that the placental hormone is capable of activating an immature ovary, one may nevertheless consider such an effect as fortuitous. Accordingly, in the theory which is proposed the active principle is considered as a pregnancy principle primarily, but as an ovary-stimulating substance it may be found effective in the activation of ovaries which are hypofunctioning.

The relationship which the hormone described in the communication bears to the so-called anterior pituitary principle found in pregnancy urine cannot be definitely stated. As yet we have confined our attention to the placenta as a source of active extracts. It appears to us more than likely that the placental hormone with which we are dealing should be present in the urine. Recently Aschheim and Zondek have taken a viewpoint somewhat similar to that of Wiesner, namely, that there are two principles which act upon the ovary—Rho I and II (Wiesner), or Prolan A and B (Aschheim and Zondek). The former is considered as œstrogenic only, in that it induces œstrus in immature animals without luteinization. Our own work lends a considerable measure of support to this point of view. In our earlier work with sulphosalicylic acid extracts and with 50 per cent acetone extracts, corpora lutea were found in the ovaries of the treated immature rats, associated with the first œstrous cycle. The purified hormone, however, has not given evidence of any luteinizing action. One point which may be of considerable significance is the observation that immature animals which have been brought to sex maturity as a result of hormone treatment show after the second or a later œstrus period definite evidence of ovulation followed by corpora lutea formation.

It was only after it had been shown that the placental extracts described were non-toxic in character and exercised no unfavourable influence in normal animals that we formulated the theory as outlined above, simply as a working hypothesis. These studies also gave us ample justification to proceed with clinical experiments, the results of which have been most encouraging. Perhaps the most important practical point of the laboratory studies has been the demonstration that this active principle is non-protein in character and is unaffected by digestive enzymes. It may therefore be administered orally.

The experience with the method of assay which has been had makes it evident that an absolute biological assay will be a matter of great difficulty. The type of method recently suggested by Coward and Burn for the assay of œstrin appears to hold the most promise. It is suggested that immature female rats three weeks of age, and not more than 35 grm. in weight, should be used. It will be necessary to use a large number of animals and to apply the statistical method of Coward and Burn to arrive at a true unit. In our work thus far only a few rats have been used at any one time, and the weight of a unit of the purified product has been found to be of the order of 0.0015 mgm. This value is not in any sense to be considered as final. It should be possible, however, at a later date, to use the purified product as a standard of reference in the standardization of extracts intended for clinical use. Absolute purity of the final product which has been described cannot be claimed until the results of further work justify such a step. However, the results which have been obtained seem to indicate that one is dealing with a pure substance.

Those workers who have attempted to obtain some measure of purification and concentration of the so-called anterior pituitary hormone in pregnancy urine have made use, for the most part, of fractions obtained by submitting concentrates to precipitation by alcohol. It is of interest to note again that the hormone of the placenta described herein is soluble in alcohol. It is altogether possible that some of this principle might be entrained or adsorbed in a precipitate resulting from the addition of alcohol to a mixture containing it. One could, however, never hope to concentrate and purify the hormone further by such methods. It is felt that if any true anterior pituitary hormone analogous in its physiological action to the pituitary implant be present in placenta, the method which we have used would exclude it even from our partially purified and concentrated extracts. It is our intention to study the physiological effects of fractions which may be separated from the precipitates and residues which have been

discarded in the preparation of the ovary-stimulating hormone described in this paper.*

We are greatly indebted to Dr. H. B. Van Dyke, of the University of Chicago, for making tests to determine the effect of the placental extract (85 per cent alcohol soluble) upon completely hypophysectomized rats. He has very kindly permitted us to quote his results, which he will doubtless publish in detail later. After two weeks of daily injections with known potent extracts, he obtained œstrus in five hypophysectomized animals. He also confirmed our results as to the absence of œstrin from the extract.

The fact that the ovary of the hypophysectomized rat has been activated by the placental extract, even though the time required was much greater than in the case of immature normal animals, is a matter of great importance. It may be viewed as evidence against the theory of placental origin of the hormone suggested in this communication. A practical point which the experiment indicates is in relation to the time required to produce the result. It is possible, therefore, that certain clinical cases of ovarian hypofunction of pituitary origin may be found to respond to treatment with the extract if the treatment is continued over some months.

The problem of standardization of the extract is a very formidable one. Lately we have found that spontaneous œstrus may occur in untreated control animals as early as twenty-six days of age. It becomes necessary, therefore, to use animals in assay work which are of such an age and weight as practically to exclude the possibility of obtaining positive results in controls. Very young rats are relatively insensitive to the hormone in our experience. Also, it has been very difficult at times to obtain clear, positive œstrus smears in rats of less than twenty-five days of age and weighing under 35 grm., even when they have been injected with known potent extracts. A phase of cornification may be obtained, but leucocytes are usually present. It is necessary, then, in many instances to confirm by post mortem and sectioning of the vagina what might be termed doubtful vaginal smears. It is possible that one may be dealing with a seasonal condition. We are desirous, however, of emphasizing the pitfalls in the biological assay, because we doubt if all who have worked in this field fully appreciate the conditions.

It is to be hoped that some satisfactory solution of the problem may be arrived at by the use of special diets or by the removal of the pituitary or thyroid gland from adult animals, with a view to rendering them acyclic.

For the moment we feel that extracts prepared by rigidly followed methods present a lesser degree of variability than does the rat assay test. The extracts which have been used clinically have therefore been appraised in terms of grams of placenta per cubic centimetre. The rat tests on these extracts have shown a variation of from one to three units per gram of original placenta.

The ultimate solution of the problem would seem to depend on the production of large amounts of final product, and a rigorous assay of this material by the use of a large number of standard animals.

The name "Emmēnin", suggested by Prof. A. B. Macallum, is proposed for the placental hormone described in this paper.

SUMMARY

1. Methods of preparing active extracts of an ovary-stimulating hormone derived from placental tissue are described.

2. Physiological studies with the hormone are described and a theory is suggested that the hormone is of placental origin.

3. The name "Emmēnin" is proposed for the hormone.

It is a great pleasure to acknowledge the great help that my colleague, Dr. D. L. Thomson, has given. I am deeply indebted to him for the survey of the literature which forms an integral part of this paper. I wish also to acknowledge the technical assistance of Mr. M. McPhail and Miss J. Williamson, who were responsible for the daily examinations of large numbers of the experimental animals. Prof. F. E. Lloyd has very kindly allowed us to use his photographic apparatus and has given us his personal assistance, for which we wish to thank him.

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NOTE

[The following details were received too late for incorporation in the body of the paper.—ED.]

It is of interest to note that an active fraction has been obtained from the precipitates removed from the original acetone extract of human placentas during the alcohol fractionation processes. This active fraction has been precipitated from aqueous solution between the ranges of 65 to 85 per cent concentration of alcohol. It has been further purified by repeated solution in water and reprecipitation by alcohol. Other methods are also being tested.

The physiological properties of this extract are such as to indicate that it contains a hormone or hormones distinctly different from emmēnin. The chief physiological property of this active fraction appears to be that of a stimulant in the female to hypertrophy of the ovary, and in the male to hypertrophy of the seminal vesicles and associated glands. The hypertrophy of the ovary is due, for the most part, to the formation of corpora lutea. The effects of long-continued administration of this particular extract are now being studied along the same lines as has previously been done with the emmēnin extract.

The chemical properties of this active fraction suggest that the hormone is of protein-like nature. Boiling of the extract has been found to result in marked loss of potency and the effect of oral administration in the dosage which has thus far been used has been negligible. A puzzling fact which will need further elucidation is the production of œstrus phenomena in the immature rat associated with the first appearance of corpora lutea in the ovaries following treatment with this luteinizing extract.

The active fraction with properties as outlined above may be readily prepared for subcutaneous administration. One realizes, however, that the use of this particular hormone can be undertaken only with the greatest of care until more is known about the ultimate effect which it will produce. There is a possibility that over-dosage phenomena may be encountered and that actual harmful end results may be produced.

The physiological properties of this luteinizing hormone are quite similar to those of the so-called anterior pituitary principle of pregnancy urine, and it is our opinion that this principle also is derived from the placenta.

We would like to emphasize that the data which have been submitted have been obtained by the use of extracts of human placentas, and we are not at all satisfied as yet that similar findings can be obtained by the use of extracts made from animal placentas, such as those of the cow or pig. The fact that certain workers have been unable to obtain the Aschheim-Zondek reactions from the pregnancy urine of these animals[30] may be of significance in this connection.

It has been suggested to the writer in certain criticism which has been made of our results, that œstrin or "theelin," as Doisy has now named the ovarian hormone, has not been entirely removed from our extract, and that the œstrus effects which have been obtained by its use may be attributable to traces of this hormone. Due to the consistent negative results which extracts of human placenta have given when tested on oöphorectomized animals, it was felt that this interfering factor had been adequately controlled. Larger doses will have to be given in the œstrin assay, over longer periods of time, to make this point clearer.

from the standpoint of metabolism and a possible putrefactive process in the intestinal tract.

It is difficult to explain the relationship between certain forms of eczema and disturbance of carbohydrate metabolism. The general hypersensitiveness of the skin to external irritants is not increased, as has been shown by Usher[6] in our clinic. Possibly, as a result of the changed metabolic activity of these individuals, abnormal metabolic products or toxic substances are formed in the tissues or intestinal tract, and these in turn act as irritants. This is a possible explanation, for which, however, no proof is forthcoming. Many persons exhibit this disturbance of carbohydrate metabolism without developing eczema (there must be an eczematous disposition), and further it must be always remembered that the occurrence of eczema in these persons may be due to a definite external irritant.

The association of eczema with disturbances of the thyroid gland is also to be noted here. Occasionally one meets the association of eczema with clinical or metabolic evidences of hypothyroidism, and the exhibition of thyroid substance results in a prompt cure of the condition.

Influences such as worry, overwork, etc., may be important factors in the production of eczema, particularly in those who in their occupation are under a constant high nervous tension. No other cause, metabolic or otherwise, is to be found in these individuals, and complete change in their surrroundings is necessary to effect a cure.

May I, in summing up, quote a short paragraph from a text-book of dermatology by Erasmus Wilson, written in 1854.

"Eczema is apt to occur symptomatically, as a consequence of some constitutional disturbance or as an effect of the application of local irritants to the surface of the skin. Of the former kind are the changes that take place in the system under hygienic influences, as during the spring and summer seasons of the year, particularly when accompanied by atmospheric vicissitudes, affections of the digestion system, as dentition, the irritation produced by unsound milk in infants at the breast, and stimulating and improper food and drinks in persons of all ages. . . . .and affections of the nervous system, as mental emotions, particularly of the depressing kind. The local causes of the disease are heat and cold, together with friction and irritation of the skin produced by whatever cause. Thus occasionally we find eczema resulting from the sun's rays, a variety which has by Willan been denominated eczema solare. It not infrequently attends the inflammation produced on the skin by the irritation of a blister, or by the application of the compound sulphur ointment or a Burgundy pitch plaster."

These observations, which were founded on clinical observations and clinical investigation, are still to-day essentially sound. We have progressed in our more exact knowledge of eczema in recent years. Ringworm, yeast, and coccal infections of the skin giving rise to eczema-like reactions, have been differentiated and taken out of the field of eczema. There is no one cause for eczema. The common factor in all eczematous individuals is an underlying hypersensitivity on the part of the skin, and, granted this disposition, a legion of internal or external irritants may be exciting agents. The specific reaction of the skin to external irritants, the factor of alimentary toxins, and the significance of the diet as it pertains to carbohydrate and protein metabolism, represent, I believe, the more important aspects in the investigation of the eczematous individual.

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Medicine is not wholly materialistic: it would discharge its functions sadly if it had nothing in view but a healthy body. Let us have that by all means if we may, but if we cannot let us bear in mind that comfort and cheerfulness do many people good besides the sick man. When prevention and cure have failed, there is much left to do which is worth doing.—*The Lancet.*

SEX HORMONES OF THE FEMALE*

A REVIEW

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SINCE the pioneer work of Berthold (1849) in demonstrating the internal secretory function of the male gonad in regard to the maintenance of secondary "sex stigmata" in birds, great advances have been made in the field of sex physiology. It has been within the last decade, however, that outstanding progress has been made in the development of this special field. It is the purpose of this article to outline, as briefly as possible, the present status of our knowledge concerning the endocrine aspect of this subject as it relates to the female. In a field where theory is so rife, it is essential that one should endeavour to keep theory and facts apart, and in the following paragraphs an earnest attempt has been made in this direction.

The earliest manifestation of endocrine activity of the gonad is found in the young rapidly differentiating and developing embryo. From the earliest elements of the Müllerian and Wolffian duct systems are developed the female and male gonad respectively. The gonad, male or female, as the case may be, proceeds, it is believed, to influence somatic development of the embryo and later of the fetus, so that even at birth certain sex characteristics are well developed. The further development and accentuation of the secondary sex qualities reaching a climax at puberty are so well known and accepted as evidences of gonadal hormone functioning that they may be dismissed at once from this discussion.

A more detailed survey of hormonal factors playing a part in sex physiology of the female may be described under the following heads: (1) the ovary; (2) the pituitary gland; (3) the placenta.

* Read at a meeting of the Sigma Xi Society, McGill University, December 18, 1929.

THE OVARY

Marshall and Jolly,[11] as early as 1906, demonstrated that the ovary produces a hormone which causes the phenomenon of œstrus. Subsequent workers — Adler,[1] Iscovesco,[8] Fellner,[5] Hermann,[7] Frank[6] and others — extended and amplified this observation. Allen and Doisy,[2] in 1923, developed an accurate method of biological assay of the ovarian hormone of œstrus, best known now as œstrin. They made extracts from pure follicular fluid, and by use of the vaginal smear method were enabled to test their product as they proceeded with its concentration and purification. They found, as did Iscovesco, that the "activity" of ovarian extracts in regard to the production of œstrus in castrated females was associated with the ether soluble or lipoid fraction, and with their new method of assay as a guide they were able to produce very concentrated extracts.

Frank, who has worked in the field for a number of years, has recently written a monograph on the "Female sex hormone", by which title he prefers to designate the hormone of œstrus. An excellent review of the literature, both laboratory and clinical, is given in this text. An even more recent monograph by Parkes[13] covers the subject most exhaustively.

Œstrin has been demonstrated elsewhere than in the ovary. Of chief interest in this connection is its occurrence in the placenta, in amniotic fluid, and in the blood and urine during pregnancy.

The physiological properties of œstrin are best manifested by injecting the hormone into a castrated adult female rat. Forty-eight hours thereafter the animal is found to be in a state of full œstrus as shown by its behaviour towards the male and by the flush of cornified epithelium in the vaginal smear. If the animal is sacrificed

marked hypertrophy of the vagina and hyperæmia and distension of the uterus will be noted. Prolonged treatment with œstrin injections is said to cause enlargement of the breasts and even the secretion of milk subsequent to the withdrawal of the treatment. Stimulation of milk secretion is denied by some workers. The effect on the male is probably anti-masculine in the main, but the hypertrophy of breast tissue in male guinea pigs has been noted.

If œstrin is injected into young and immature rats or mice the phenomenon of œstrus is induced as it is in the castrate, also the same effect is obtained in the öophorectomized immature animal. A point of great interest in the physiology of œstrin is its *apparent non-effect upon the intact normal ovary.* The injection of œstrin during pregnancy results in abortion if the dosage administered be adequate. The amount required in the later stages is much greater. Œstrus may also be induced by œstrin in the lactating animal. It is claimed that œstrus changes may be induced in the senile animal by injection of the hormone. The ovary, however, is not stimulated and ovulation does not occur.

THE PITUITARY GLAND

It is apparent that since the hypertrophy of the genital tract at each period of œstrus is due to a specific stimulus afforded through the functioning of the hormone œstrin, the ovary must liberate this internal secretion at periodic intervals. The question therefore arises as to what controls the periodicity of the ovary in this one respect at least. This question has been largely answered by the conclusive demonstration in the work of Smith and Engle,[14] and Zondek and Aschheim[17] that the phenomenon of ovulation is in large measure controlled by the secretion of the anterior lobe of the pituitary gland. The question as to how the pituitary gland functions as it does remains for the present unanswered.

Smith and Engle, and Zondek and Aschheim, by means of fresh intramuscular implants of anterior pituitary substance, succeeded in demonstrating intense stimulation of the immature ovary of rats and mice. The effect consisted in marked hypertrophy of the infantile gland due to the rapid growth of Graafian follicles. The development of the follicles appeared to follow a normal course, and normal but superovulation resulted. But of even greater interest was the production of premature puberty and all the phenomenon of œstrus, opening of the vagina, cornification of the vaginal mucous membrane, enlargement, engorgement and distension of the uterus. This latter result was undoubtedly due to the liberation of œstrin from the ovaries of the immature animal, stimulated to activity by the anterior pituitary hormone.

The recent experiments of Parkes[13] in which follicular ablation was produced by means of x-rays supply evidence that the periodicity of œstrus is not necessarily governed by the periodic maturation of follicles.

Further evidence that the pituitary gland has a profound influence on the gonad is found in the results of hypophysectomy. Removal of the hypophysis causes cessation of ovarian development and activity.

If one considers the normal ovarian cycle (maturation of the Graafian follicle resulting in rupture and escape of the ovum, to be followed immediately by the development of the corpus luteum from the old follicle) and the subsequent history of the corpus luteum, depending as it does on the fate of the shed ovum, one sees presumptive evidence, at least, of endocrine activity other than that thus far discussed. Many of the presumptive functions of the corpora lutea have of late years been definitely proved as entities. Functioning corpora lutea have been shown to inhibit ovulation and œstrus changes in the genital tract. The recent work of Corner[3] has demonstrated that the progestational proliferation of the uterine mucosa is a function of the corpus luteum and he has succeeded in producing this effect by means of extracts. He has also shown the importance of the corpus luteum in maintaining the nutrition of the uterus of the impregnated animal by carrying rabbits through pregnancy which had been öophorectomized following impregnation.

The development of the mammary glands from the condition in which they are found at œstrus to that at the end of the luteal phase is another function of the "yellow body".

Since there is a great deal of species difference in regard to the phenomena of sex, it is rather difficult to correlate the conditions as found in the human female with the œstrus cycle as manifested in the various lower species. For example, ovulation and œstrus are as a rule

synchronized in the lower animals, whereas in the human individual ovulation has been abundantly proved to be an inter-menstrual phenomenon occurring probably on the fourteenth day following the beginning of the last menses. The rabbit and ferret only ovulate following copulation or mechanical stimulation of the cervix. Immediately following ovulation in these species, the corpora lutea develop, and as the life time of the corpora is, in the absence of impregnation in the rabbit, about two weeks, the condition of pseudo-pregnancy can be studied to advantage here. Pseudo-pregnancy is apparently entirely a corpus luteum phenomenon. It consists, in the rabbit, of considerable mammary gland and uterine hypertrophy. It also represents a period of sensitization of the uterus because mechanical irritation, as from a foreign body introduced into the uterus, leads to the formation of a tumour-like growth, the deciduomata first described by Loeb.[9]

Following atresia of the corpora lutea retrogressive changes in the mammary gland and uterus occur. Reasoning from such observations it has been suggested that menstruation, which is so markedly a human characteristic, is really the termination of what might be termed a pseudo-pregnant condition, due to atresia of the corpus luteum which develops and flourishes for ten or twelve days following ovulation. In support of this theory there is the evidence that removal of a fresh corpus luteum is followed very shortly by the menstrual flow. Marshall[10] has suggested that menstruation represents pseudo-pregnancy and pro-œstrus degeneration telescoped into one.

There is a certain amount of evidence that the anterior lobe of the pituitary gland may produce a second hormone which has an inhibitory effect upon the ovary. Evans[4] found that the injection of his alkaline extract of the anterior lobe, which contains the growth principle, caused rat ovaries to become almost completely luteinized with concomitant cessation of periods of œstrus. Teel,[15] by injecting a similar extract during pregnancy, was able in the rat to prolong the gestation period from two to six days beyond the normal. Wiesner[16] also claims that there is a second and inhibitory factor in the anterior pituitary and also in the placenta, which induces luteinization of follicles and a pseudo-pregnancy reaction in the uterus and vagina.

THE PLACENTA

Zondek and Aschheim found that implants of placenta produced similar effects to anterior pituitary implants or injection of anterior pituitary emulsion. They also found that the urine of pregnant women which had been freed from œstrin by extraction with ether contained anterior pituitary hormone. Similarly, the blood during pregnancy has been shown by them to produce an anterior pituitary effect when injected into ammature mice. Wiesner[16] has worked extensively with placental extracts, and claims the coexistence of two hormones therein, one stimulatory to the ovary, the other causing inhibition of œstrus and a pseudo-pregnancy reaction. The placenta is therefore rich in two hormones—œstrin; a pituitary-like ovarian stimulant; and, possibly, a third inhibitory principle.

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THE OVARY-STIMULATING HORMONE OF THE PLACENTA

PRELIMINARY PAPER

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IT has been abundantly proved that the placenta contains the hormone of œstrus. This hormone, "œstrin", or the "female sex hormone", as it is designated by Frank,[5] was first studied in detail by Allen and Doisy.[1] They developed a method for the accurate biological assay of extracts containing the active principle. The assay is dependent on the characteristic property of the hormone to produce the phenomenon of œstrus in a fully castrated female rat. Since their original work on follicular fluid as a source of this œstrus-producing ovarian hormone, œstrin has been abundantly demonstrated elsewhere than in the ovary. Placenta, amniotic fluid, and the urine of pregnancy have been shown to contain very considerable amounts of the hormone.

Prior to the development of more accurate methods of assaying for œstrin, many earlier workers had proved that lipoidal extracts of placenta when injected into young females caused premature maturity of the uterus and vagina. A similar result was obtained with adult castrates.

Since œstrin is most readily obtained by taking advantage of the fact that it is freely soluble in fat solvents, and can be removed completely from aqueous suspension by the use of ether, workers in this field have for the most part confined their investigations to the lipoid fraction of tissues or fluids studied. The demonstration that a water-soluble hormone having physiological properties quite distinct from œstrin may occur separate from or in conjunction with the latter is an outcome of the independent work of Smith and Engle[9] and of Zondek and Aschheim[11] on the ovary-stimulating action of implants of anterior pituitary substance. These investigators were able to show the most dramatic results in immature female rats and mice following the intramuscular injection of fresh anterior pituitary gland or saline suspensions of the same. The effect of such treatment is to cause a most rapid development of the immature ovary. Smith and Engle report that the ovary of the experimental rat may be ten-fold the size of that of the control, and nineteen-fold in the case of the treated immature mouse. The increase in ovarian tissue thus produced is due for the most part to the rapid maturing of Graafian follicles. These apparently mature in a normal manner and superovulation results. But even of greater interest is the fact that as a result of the stimulation of ovarian activity, œstrin is liberated, producing its typical effects, *viz:* hypertrophy of the genital tract and the phenomenon of œstrus. The work of these authors has therefore established that a hormone of the anterior pituitary gland can cause by direct stimulation of the ovary (liberating œstrin) all the effects of œstrin *per se*. There is this sharp distinction between the anterior pituitary principle and œstrin—anterior pituitary hormone has no effect on the castrate, whereas œstrin acts just as effectively in the castrate as in the normal female.

Zondek and Aschheim later demonstrated that implants of 0.1 grm. of placenta produced ovulation in immature mice. Blood serum and the urine of pregnancy were found to be similarly active, in doses of 0.5 and 1 to 2 c.c. respectively. They have also detected the ovarian stimulating principle in decidua, in the corpus luteum of pregnancy, in tubal mucous membrane, and in the blood of the new-born. They have prepared an œstrin-free product from the urine of pregnancy and have developed a method of biological assay of the principle dependent upon the production of hæmorrhagic follicles in the ovaries of 6 to 8 grm. immature mice. The pioneer work of Smith and Engle, and of Zondek and Aschheim, on the ovary-stimulating hormone of

the anterior pituitary gland has been confirmed by Fels,[4] Brouha and Simonnet,[3] Loewe,[6] and Siegmund.[7]

Dr. Wiesner,[10] of the Department of Animal Breeding of Edinburgh University, has recently succeeded in preparing potent aqueous extracts of the ovary-stimulating hormone from human placentæ. Wiesner's method consists in extracting the fresh placenta or placental press-juice with sulphosalicylic acid. This has the advantage of giving almost immediately a practically protein-free extract, which, after neutralization and clarifying by adequate filtration, may be injected directly. It has the disadvantage, however, that it still contains sulphosalicylic acid, or its salts, and does not readily lend itself to concentration processes. Dr. Wiesner visited the writer's laboratory in September, 1929, and demonstrated in a single but convincing experiment the effectiveness of the sulphosalicylic acid extract of fresh human placenta in producing premature maturity in the young rat. At Dr. Wiesner's very urgent request the writer took up the problem of the concentration of the premature maturity producing principle in the placental extract. A considerable number of experiments were therefore undertaken with sulphosalicylic acid extract of placenta and Dr. Wiesner's claims for the effectiveness of this extract were amply confirmed. At times, an immature female rat could be made to develop full œstrus and ovarian hypertrophy (confirmed by microscopic sections) on the fifth day following the injections of an amount of extract equivalent to 1/3 grm. of placenta. It was found best in practice to give two injections, one on the first and one on the second day, and to sacrifice the test rat on the fifth day.

It soon became apparent that the presence of the sulphosalicylic acid in the extract presented a most formidable barrier to further concentration and purification of the active principle. A variety of methods of extraction and fractionation were therefore resorted to and as a result it has been found possible to attain great concentration of the active principle. It has been obtained free from protein, salt, lipoid and œstrin, and in the form of an aqueous solution it may be administered either subcutaneously or orally. It is possible to place the equivalent of 100 grm. of placenta in 1 c.c. of water with a relatively small loss of the active principle contained in the original tissue. The potency of any extract may be ascertained fairly accurately in terms of rat units by making use of the slightly modified method of Zondek and Aschheim referred to above. The minimal amount given in two injections on successive days to produce full œstrus in immature rats three to five weeks old on the fifth day may be taken as the unit. It is also essential that the extract should be without effect on castrates.

Whether, as it has apparently been assumed, the ovary-stimulating hormone which has been demonstrated in anterior pituitary implants, in anterior pituitary extracts, in the blood and urine of pregnant women, and in the placenta, is the same in each instance remains for the present an academic issue. Why the pituitary gland should liberate this secretion so promiscuously during pregnancy, so that tens of thousands of rat units are lost in the urine, and why the placenta should act as a storehouse, are questions which must remain unanswered for the present. The writer prefers to hold the theory that in the case of the placenta the hormone with which we are dealing is actually elaborated therein.

Smith[8] has stated that anterior pituitary gland is ineffective by the oral route. A chance laboratory technical error gave a clue to the fact, later established, that the placental hormone under course of study was quite effective when administered by mouth. Certain control immature animals which were caged with injected animals were observed to show œstrus. Since there is nearly always an appreciable leakage of the injected fluid at the point of injection, and as rats are very prone to lick one another's coats, it seemed that this was the obvious explanation for the observed result in this case. Systematic feeding experiments were carried out. It was found best to administer the extract by mixing it with finely ground lean meat, which absorbs it almost completely, and which the animals eat ravenously. The amount of extract thus effective was surprisingly small. The equivalent of one gram of fresh placenta fed daily as an aqueous œstrin-free extract has produced œstrus on the fifth day. Much larger amounts produce the same effect.

In order to ensure the conviction that the efficiency was unimpaired by digestive juices, the œstrin-free extract has been treated with gastric

juice of known peptic activity for as long as seventeen hours. No loss of potency was observed. Similar results were also obtained after tryptic digestion during a period of two hours.

The results obtained by oral administration and the digestion experiments outlined above would seem to indicate one of two things—either the placental ovary-stimulating hormone is essentially different from that of the anterior pituitary, or the latter has not as yet been obtained in a sufficiently concentrated form to show similar properties.

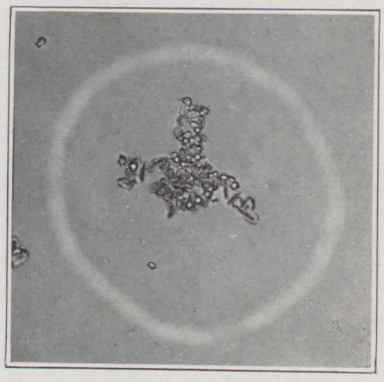

FIG. 1.—Photomicrograph of a potent crystalline fraction.

In order to study adequately the ovary-stimulating factor in placenta, it is necessary to employ a very large white rat or mouse colony. The albino rat has been used almost exclusively in this work, and breeding has been so arranged that litters of immature females of three to four weeks of age are available at all times. It is essential that both the breeding stock and the young be exceptionally well nourished. This is assured by feeding the basic diet of Sherman (whole wheat flour two parts, and powdered whole milk one part), supplemented by brewer's yeast, wheat germ, and a liberal amount of raw, lean meat.

A brief account of the more important findings to date in this research will now be given.

1. Immature female rats from 35 to 60 grm. in weight, and from 3 to 5 weeks of age, have been used according to a slightly modified technique of Aschheim and Zondek and of Wiesner, to assay biologically the content of the ovary-activating hormone in placental extracts. This method of assay has made possible the concentration and purification of the active principle by means of fractionation processes, to be described at a later date, to the point where one rat unit may be represented by 0.01 mgm. of dry substance. Certain micro-crystalline fractions of great potency have been obtained, but it is impossible to state as yet whether such fractions are pure chemicals. It is of special interest that immature white rats thus stimulated by the placental hormone to a state of œstrus as a rule become cyclic. Nine of these have also been impregnated by an active male in a normal manner.

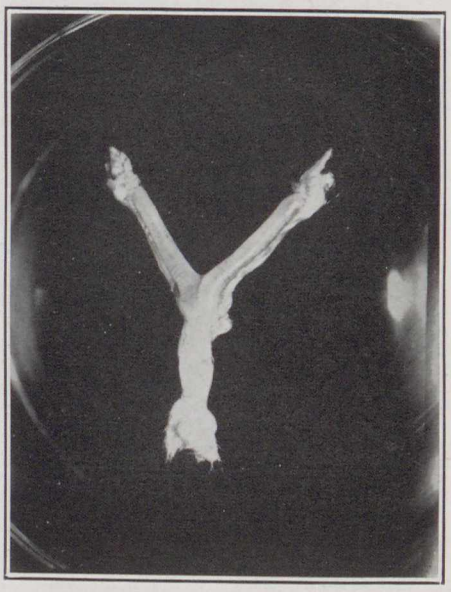

FIG. 2.—Genital tract of rat injected at 27 days of age with a total of 2 c.c. of an extract made from the crystalline fraction shown in Fig. 1. Autopsy on fifth day.

FIG. 3.—Control for Fig. 2.

If injected immature rats are sacrificed at various periods following the administration of the hormone, one notes first the rapid development of the Graafian follicles, associated with the changes in the mucous membrane of the vagina leading up to the œstrus desquamation of cornified epithelium. Corpora lutea then appear and one finds that the vaginal mucous membrane has now changed from the squamous to the cuboidal cell type. In our experience corpora lutea are not found in the ovaries of immature control rats. It is possible, therefore, to substitute the finding of corpora lutea in the ovary of immature animals injected with the placental hormone for the well-known œstrus phenomena usually made use of in biological testing. When the appearance of young corpora lutea is made the basis of a positive reaction the test animal may be sacrificed on the sixth or seventh day following the injection, or even later. It is possible, however, to have corpora lutea appear earlier, since a positive vaginal smear may on occasion be noted as early as the third day.

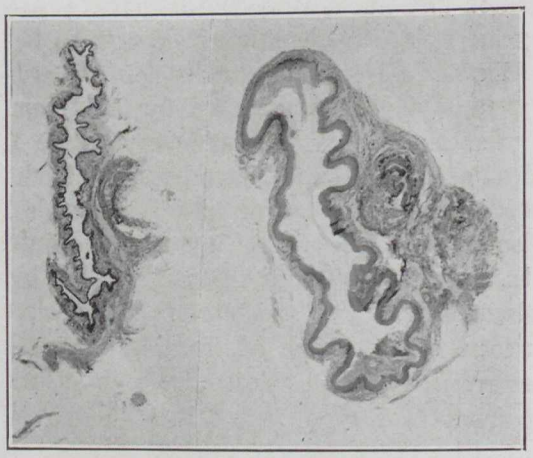

FIG. 4. — Cross section of vagina of immature rat.

FIG. 5.—Cross section of vagina of immature rat treated with placental hormone.

2. It has been shown that the same physiological effects may be produced in immature rats by oral administration of the hormone as by subcutaneous injection. The dosage by mouth necessary to produce these effects may not be more than two or three times the effective subcutaneous dose.

3. The hormone has been shown to be effective after moderate periods of exposure to the action of the digestive enzymes, pepsin and trypsin.

4. Injection of the active extract into adult castrates over a period of weeks is without effect. Injection of adult but vigorous normal females with two rat units daily has had very little effect on the normal œstrus cycle. In these experiments the animals were first submitted to a control period during which, by the taking of daily vaginal smears, the individual cycles were established. Œstrus occurs in most adult animals at regular intervals of four to six days. Apart from a slight extension of the period of cornification of the vaginal epithelium no effect was noted. Two pregnant animals receiving similar dosage daily, carried through a normal pregnancy, labour and lactation period, and, even though the injections were continued bi-daily, the animals again became pregnant following the introduction of a vigorous male, and a second time delivered a normal litter in the normal time. One would anticipate in the light of Smith's work, in which he caused termination of pregnancy in rats by pituitary transplants, that abortion might be induced by the above treatment. This may be a matter of dosage and the experiments are being repeated, using much larger doses in terms of rat units.

The injection of 12 rat units daily for three weeks produced no ill effect in a 2-kilo rabbit, and no marked change in the chemical constitution of the blood, apart from a slight increase in cholesterol.

5. The laboratory investigation making possible the production of a standardized extract containing the ovary-stimulating hormone factor, and its physiological effects having been studied in sufficient detail in certain animals, seemed to justify the view that clinical investigation of the effectiveness of the extract might now be started. On *a priori* grounds one may reason that only those individuals who give definite evidence of hypoactivity of the ovary may be expected to receive benefit by the placental hormone. Therefore, in an experimental clinical study only such types of cases should be treated. Dr. A. D. Campbell is collaborating in this work and already a few typical patients with hypo ovarian signs and symptoms have been placed under treatment. The results so far obtained have been encouraging. (See the following paper in this issue).

One must remember that luteinization of the ovary has been produced by certain alkaline

pituitary gland extracts, furthermore that Wiesner has demonstrated luteinization following injection of his placental extract. It is possible, therefore, that overdosage might in the end result in sterilization, due to excessive lutein formation. For this reason, any clinical trials must necessarily be carried on with the greatest caution.

6. The laboratory results reported in this preliminary communication are based on assay studies of 150 immature rats, as well as on 12 digestion experiments and 9 feeding experiments. Upwards of 500 microscopic preparations have been made and examined.

It is a great pleasure to acknowledge the kindly interest and co-operation of Prof. W. W. Chipman, and to thank him for placing the material of the Royal Victoria Maternity Hospital at our disposal. Our thanks are also due to Dr. S. Langevin and the Sisters of the Misericordia Hospital for kindly supplying material.

We wish especially to thank Dr. Wiesner for bringing the problem to this laboratory for investigation.

We also desire to acknowledge the most valuable technical assistance of Mr. M. McPhail, of Miss J. Williamson, and of Mr. A. A. Long. We are also indebted to Professor F. E. Lloyd for assistance with the photography.

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ON THE CLINICAL USE OF THE OVARY-STIMULATING HORMONE OF THE PLACENTA

PRELIMINARY REPORT

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SINCE it has been shown* that the "ovary-stimulating hormone of the placenta" has a specific effect in activating the ovary of the immature rodent, it has been deemed advisable also to carry out clinical experiments with this substance. These experiments obviously demanded great caution, and every care was taken in carrying them out.

Selected cases of ovarian hypofunction were therefore placed under treatment by oral administration of the extract. At first a very small dose was given, but it was soon discovered that the dosage could be greatly increased.

It is too early to make a definite pronouncement upon the value of this treatment, for numerous clinical factors have yet to be considered, as well as the question of dosage and duration of administration. It may be said, however, that definite results of a most encouraging character have been obtained in five cases of oligo-menorrhœa, in two cases manifesting distressing menopausal symptoms, and in two cases of dysmenorrhœa.

The following case reports are submitted from this series.

CASE 1

A girl, unmarried, Canadian, aged 17, who complained of amenorrhœa for three years.

Personal history.—Menstruation had begun at the age of 14, appearing as a slight "spotting" on two occasions within the first year, at intervals of four months. For the past two years she had had so-called nocturnal epilepsy, but there had been no headache, no symptoms of indigestion or constipation, no pelvic pain, and no leucorrhœa.

General examination.—She was of an exceedingly well developed athletic type. The integumentary and glandular systems were negative. The general distribu-

* See this issue, page 215.

tion of hair was normal. The eye grounds were normal. X-ray examination of the skull showed a normal sella turcica.

Pelvic examination.—The hair on the vulva was rather sparse; the perinæum was non-scaphoid; the hymen was intact. Rectal examination showed the uterus to be small, and of normal shape and position. The cervix was small and rather long.

Treatment.—On November 30, 1929, a dilute extract of placenta was administered by mouth. This was gradually increased. In all, 500 rat units were given. It was discontinued on December 22nd, on which date menstruation began, lasting four days, with no pain or vomiting or other untoward symptoms. Menstruation reappeared spontaneously on January 17, 1930, lasting four to five days, and being associated with no untoward symptoms. She had received no extract since December 22nd.

CASE 2

A Canadian, married, aged 26, complaining of nervousness, loss of weight, and comparative amenorrhœa.

Personal history.—She had had a curettage after abortion one year ago, during the second month of gestation, since which time the menses had become scanty, lasting only part of a day.

Menstruation had begun at the age of 13, and was of the four-day type, occurring every 28 days, and causing no special symptoms. Her personal history contained nothing of importance.

Physical examination, on December 14, 1929, showed her to be thin and nervous, weighing 119 lbs., and showing signs of early but acute hyperthyroidism. Her basal metabolic rate was +29. The general physical examination was otherwise negative.

Pelvic examination.—Vagina marital; cervix normal; uterus small and hard.

Treatment.—On December 14th she was given five c.c. of the extract by mouth, three times daily (one c.c. is equal to five rat units). On January 11, 1930, she menstruated three full days. On January 17th the extract was discontinued. On January 29th the basal metabolic rate was found to be +1. Her weight was now 127 lbs., and her nervous symptoms had disappeared.

CASE 3

A Canadian, unmarried, aged 28, complaining of dysmenorrhœa.

Personal history.—She had had scarlet fever at the age of five, measles at ten, and influenza at 16. Appendectomy had been performed at 18.

Menstruation had begun at the age of 13½ years, and appeared regularly every 28 days. It was accompanied each time by intense abdominal pain, at times necessitating a sedative for relief. Vomiting also accompanied each epoch.

Physical examination.—She was of excellent physique, and the general examination was negative.

Pelvic examination.—Rectal examination showed the hymen to be intact and the cervix to be normal in length. The uterus was acutely anteflexed. Her last menstrual period had been December 26, 1929.

Treatment.—On January 9, 1930, she was given the extract by mouth; 75 rat units were administered daily for eight days. She menstruated from January 20th to the 25th, and for the first time in her life the menstruation was not accompanied by either pain or vomiting.

During the course of treatment certain patients have manifested symptoms of nausea, whilst others experienced some discomfort in the pelvic region. Others stated that they had experienced dreams of a vivid and unusual character. Severe headache and mental depression have also occurred. As a rule the patients voluntarily expressed a feeling of well-being in from four to five days after withdrawal of the extract.

It is interesting to note that in view of the well established fact that the extract is without effect on the öophorectomized rodent, clinically, one cannot expect relief from menopausal symptoms after pan-hysterectomy. One such case was studied, with the anticipated failure to obtain any beneficial results.

COMMENT

The suggestive results obtained in this small group of cases have encouraged us to continue the experiments in the clinical use of this hormone on a more elaborate scale. Our experience thus far has demonstrated that patients should be selected, hospitalized and thoroughly investigated before and during the administration of this percental extract. A detailed report of such clinical studies will be made at a later date.

It is hoped that such studies will throw new light upon the problems of ovarian dysfunction and hyperthyroidism; and in addition, that the study of the ovary-stimulating hormone in the blood, and its distribution in the placenta of both the normal and the toxæmic pregnant woman, will help to unmask the etiology of certain of the so-called toxæmias of pregnancy.

REVOCABLE STERILIZATION OF THE FEMALE.—Haberlandt since 1919, has been experimenting on the problem of producing temporary sterility in female animals. Subcutaneous transplantation of ovaries from pregnant rabbits and guinea-pigs produced temporary sterility in these. The effect is thought to be brought on by the formation of a hormone in the transplanted corpus luteum, which inhibits follicle maturation. After resorption of the transplanted ovaries the animals became pregnant and gave birth to mature, normally developed, living young. Sterility could be obtained for two to three months. Haberlandt obtained identical results by the daily subcutaneous injection of certain ovarian and placental extracts on the market. He is convinced of a hormonal action in securing temporary sterility in these animals. It is not inconceivable, therefore, that, when we know more of ovarian hormones and when ovarian extracts are really active, Haberlandt's work on animals may be of practical value in producing the temporary or revocable sterilization of women—*Zentralbl. f. Gynäk.* **51:** 1418, 1927.